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

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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.

MonoMAC syndrome is a rare immunodeficiency syndrome caused by heterozygous mutations in GATA2. It is characterized by profound monocytopenia, mycobacterial infection, and lymphatic abnormalities. Here, we present a case of MonoMAC syndrome in a patient with a GATA2 mutation, who presented with fever of unknown origin, recurrent mycobacterial infections, and lymphatic abnormalities.

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.

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Lymphoid cells: typically natural killer and B cells. CD4+ lymphopenia (including CD4+ T-regulatory cells) has been described.

Myeloid cells: monocytes and dendritic cells.

Cytopenias
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- Lymphoid cells: typically natural killer and B cells. CD4+ lymphopenia (including CD4+ T-regulatory cells) has been described.
- Other: anemia, neutropenia, and thrombocytopenia associated with myelodysplastic syndrome or acute myeloid leukemia.

Noninfectious complications
- 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
- Cytopenias
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Infections
- Nontuberculous mycobacterial infections
  - Typically *Mycobacterium avium* complex
  - Other slow-growing species: *M. kansasi*, *M. scrofulaceum*, *M. bovis*, *M. szulgai*
  - Rapid-growing species: *M. fortuitum*, *M. abscessus*, *M. massilense*
- 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.

Table 1. Main Characteristics of MonoMAC Syndrome

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Cytophenias
- Myeloid cells: monocytes and dendritic cells.
- Lymphoid cells: typically natural killer and B cells. CD4+ lymphopenia (including CD4+ T-regulatory cells) has been described.
- Other: anemia, neutropenia, and thrombocytopenia associated with myelodysplastic syndrome or acute myeloid leukemia.

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 tuberculin skin test (20 mm) but the QuantiFERON-TB Gold IN-Tube test were all negative. Serum immunoglobulin levels 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 MonoMAC syndrome. Genetic testing found a heterozygous mutation in GATA2 (c.1186C > T; p.R396W) confirming the diagnosis of MonoMAC syndrome. 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].

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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 granulocyte macrophage colony-stimulating factor (GM-CSF) receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet 2003; 34:70–74.

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.

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

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