

Multiple Simultaneous Infections With Nontuberculous Mycobacteria in the Setting of *GATA2* Mutation and Myelodysplastic Syndrome

Hussam Tabaja,¹ Kelsey L. Jensen,² Christina G. Rivera,³ Anisha Misra,⁴ Rajiv K. Pruthi,⁵ and Paschalis Vergidis^{1,6}

¹Division of Public Health, Infectious Diseases and Occupational Medicine, Mayo Clinic, Rochester, Minnesota, USA, ²Department of Pharmacy Services, Mayo Clinic Health System, Austin, Minnesota, USA, ³Department of Pharmacy Services, Mayo Clinic, Rochester, Minnesota, USA, ⁴Division of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota, USA, and ⁵Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

GATA2 mutation can result in profoundly reduced monocytes, dendritic cells, natural killer cells, and B cells, and is associated with a predisposition for recurrent and disseminated nontuberculous mycobacterial (NTM) infections and myelodysplasias. Herein, we describe a unique case of 3 simultaneous disseminated NTM infections in a patient with *GATA2* mutations.

Keywords. nontuberculous mycobacteria; *Mycobacterium avium*; *Mycobacterium abscessus*; *Mycobacterium simiae*; *GATA2* mutation.

The incidence of infections caused by nontuberculous mycobacteria (NTM) is increasing worldwide due to acquired or iatrogenic immunosuppression [1, 2]. In this report, we share our experience with an unusual case of 3 simultaneous disseminated NTM infections in a patient with guanine-adenine-thymine-adenine 2 (*GATA2*) mutation and myelodysplastic syndrome.

CASE REPORT

An 81-year-old man was admitted for scattered skin abscesses. His comorbidities included coronary artery bypass, arthroplasties, and sensorineural hearing deficit. His sister had leukemia at age 65. Family history was otherwise unremarkable. He developed fevers of 6 months duration. He later had transaminitis and anemia. A liver biopsy showed mildly active hepatitis with

focal lobular histiocyte clusters/small granulomas. Nodular skin lesions appeared over his forehead, extremities, and gluteal region (Figure 1). Chest computed tomography (CT) showed scattered pulmonary nodules. A positron emission tomography CT showed fluorodeoxyglucose-avid lesions in skin and soft tissue, brain, and lungs. A punch biopsy of skin demonstrated dense granulomatous and suppurative inflammation and stained positive for acid-fast bacilli using acid-fast and Fite stains. Tissue cultures grew *Mycobacterium abscessus* complex, identified by matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS). However, he grew *Mycobacterium avium* complex (species *avium*) and *Mycobacterium simiae* from separate blood cultures. The microbiology laboratory confirmed no identification errors. *Mycobacterium abscessus* complex grew from typical dry and nonchromogenic colonies and *M simiae* grew from typical translucent yellow colonies. Both *M avium* and *M simiae* isolates were confirmed via 16s ribosomal RNA (rRNA) Sanger sequencing.

The patient had monocytopenia and lymphopenia. Bone marrow biopsy showed evidence of chronic myeloid neoplasm, rare circulating blasts, and marked hypercellularity, with features of myelodysplastic syndrome (MDS) with multilineage dysplasia with approximately 5% bone marrow blasts and 2% circulating blasts. Cytogenetic testing demonstrated complex changes; of 20 metaphases, 4 had t(1;6)(q21;p21) and all metaphases had a (13;14) constitutional Robertsonian translocation (the latter is not a clonal abnormality). Next-generation sequencing was performed on extracted DNA from bone marrow aspirate and core biopsy as previously described at our center (OncoHeme, Mayo Clinic) [3]. This revealed 2 *GATA2* gene variants: Chr3(GRCh37):g.128204894_128204895del, NM_001145661.1(*GATA2*):c.546_547del; p.Pro183* (6% allele frequency) and Chr3(GRCh37):g.128200134CCTT>C; NM_001145661.1(*GATA2*):c.1168_1170delAAG; p.Lys390del (56%). Mutations in *ASXL1*, *MPL*, and *U2AF1* were also detected.

Mycobacterium abscessus complex has historically proven itself to be more difficult to treat; hence, antibiotics were tailored toward *M abscessus* complex while retaining at least 2 drugs active against *M avium* and *M simiae* (see Table 1 for susceptibilities): oral azithromycin 500 mg daily and intravenous (IV) imipenem 1 g twice daily, IV tigecycline 50 mg daily, and IV amikacin 15 mg/kg 3 times weekly. Amikacin target peak (C_{max}) and trough levels were 35–45 µg/mL and <5 µg/mL, respectively. Imipenem was later switched to IV cefoxitin 3 g every 12 hours due to concern for drug-induced thrombocytopenia. Constitutional symptoms persisted and new skin lesions appeared. Amikacin C_{max} target was increased to 45–60 µg/mL

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Correspondence: Paschalis Vergidis, MD, Division of Public Health, Infectious Diseases and Occupational Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA (vergidis.paschalis@mayo.edu).

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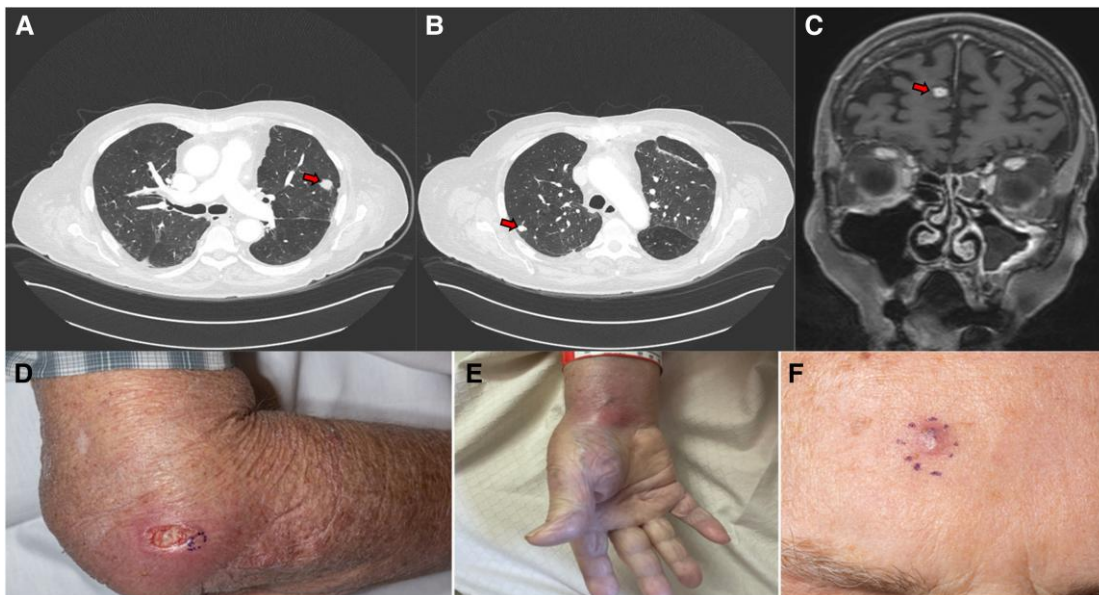


Figure 1. A and B, Scattered pulmonary nodules (red arrow). C, Single isolated brain nodule (red arrow). D, Nodular skin lesion over lateral elbow with ulcerated center. E, Right wrist swelling and redness; magnetic resonance imaging of the wrist with and without intravenous contrast (not shown) revealed marked synovitis at the radiocarpal joint and extensor and flexor tenosynovitis. F, Nodular skin lesion over the forehead.

and oral clofazimine 50 mg daily was added. After start of treatment, repeat mycobacterial blood cultures remained negative. Skin lesions stabilized and fevers resolved, and he was discharged to a transitional care unit. The anticipated therapeutic program was 2–3 months of a 5-drug regimen followed by 9–10

months continuation with 2–3 drugs (oral azithromycin, oral clofazimine, with or without oral linezolid or IV ceftioxin). After discharge, the patient gradually declined and became transfusion dependent. He was not a candidate for bone marrow transplant. He was later transitioned to comfort care,

Table 1. Antimicrobial Susceptibility Test Results for Isolated Nontuberculous Mycobacteria and Our Therapeutic Approach

Antimicrobial Agent	<i>Mycobacterium abscessus</i> Complex		<i>Mycobacterium avium</i>		<i>Mycobacterium simiae</i>	
	MIC, µg/mL	Interpretation	MIC, µg/mL	Interpretation	MIC, µg/mL	Interpretation
Amikacin	16	S	8	S	16	S
Amikacin (liposomal inhaled)	8	S
Ceftioxin	64	I
Ciprofloxacin	>4	R ^a	>8	R ^a
Clarithromycin	0.25	S ^{b,c}	2	S ^c	4	S ^c
Clofazimine	0.25	NI	0.12	NI	0.12	NI
Doxycycline	>8	R	>8	R
Imipenem	16	I
Linezolid	8	S	32	R	32	R
Minocycline	>8	R
Moxifloxacin	4	R	>4	R	1	S
Rifabutin	1	S
Rifampin	>4	R
Tigecycline	0.25	NI
Tobramycin	16	R
TMP-SMX	4/76	R	>4/76	R

Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; NI, no interpretation; R, resistant; S, susceptible; TMP-SMX, trimethoprim-sulfamethoxazole.

^aCiprofloxacin and levofloxacin are interchangeable, but both are less active in vitro than moxifloxacin.

^bNo inducible clarithromycin resistance detected.

^cClarithromycin is the class representative for the macrolides (ie, clarithromycin, azithromycin, and roxithromycin).

antibiotics were stopped, and he eventually succumbed to his illness after 3 months of treatment.

DISCUSSION

GATA2 gene is located on chromosome 3q21 and encodes a master transcription factor that is key to the proliferation and maintenance of hematopoietic stem cells and lymphatic angiogenesis [4, 5]. *GATA2* mutations can lead to a state of haploinsufficiency [5]. Immunodeficiency with increased susceptibility to human papillomavirus and NTM, and a predisposition to MDS/acute myeloid leukemia, protein alveolar proteinosis, and lymphedema is the clinical hallmark [6]. However, patients with *GATA2* mutations demonstrate clinical heterogeneity (Supplementary Figure 1). Mutations at different locations of *GATA2* lead to different syndromic phenotypes such as monocytopenia and *M avium* complex (MonoMAC) syndrome, Emberger syndrome, and dendritic cell, monocyte, B, and NK lymphoid deficiency syndrome [5]. Symptoms mostly occur in adolescence to early adulthood [6]. In 1 series, the median age at disease onset was 18.6 years, and the probability of remaining without symptoms at age of 40 years was as low as 8% [7]. This high penetrance was also seen in another study where only 7% of individuals with *GATA2* mutations remained asymptomatic during follow-up [6]. To date, >100 different germline *GATA2* mutations were reported in >400 cases [5]. Mutations can be grouped into 3 types: (1) missense mutations and in-frame deletions in the C-terminal zinc finger domain; (2) nonsense mutations, frameshifts, and large deletions resulting in null alleles; and (3) mutations in regulatory enhancer region of intron 5 [6]. Mutations that affect *GATA2* transcript integrity can lead to severe disease while regulatory mutations that preserve transcript integrity may have variable penetrance and later disease onset [5, 6].

Mutations in *GATA2* can be germline or somatic. Germline mutations follow an autosomal dominant pattern of inheritance, and their clinical manifestations typically occur in family cohorts, although sporadic cases have been described [8]. Patients may present with primary bone marrow failure syndrome, such as aplastic anemia or MDS [5]. Alternatively, they may present with acute myeloid leukemia at a young age. Patients typically have hypocellular bone marrow, which contrasts with the hypercellular bone marrow usually seen with de novo MDS [6]. Up to 80% of patients with germline *GATA2* mutations may develop such hematologic malignancies [7]. Patients may also have a simultaneous or stand-alone primary immunodeficiency syndrome with profoundly reduced monocytes, dendritic cells, NK cells, and B cells [5]. Reported rates for NTM infections vary widely [7, 9, 10]. For example, in early studies of MonoMAC syndrome, up to 78% of patients had NTM infections [9]. On the other hand, a much lower rate of 15% NTM infections was detected in a

larger and more contemporary study of germline *GATA2* mutations [7]. In the latter study, the estimated risk for all mycobacterial infection was 9% at age 20 years and 42% at age 40 years [7].

In contrast to germline mutations, somatic *GATA2* mutations are acquired after conception. They are poorly described in the literature but may occur in 1%–4% of patients with sporadic myeloid malignancies [11]. Prior studies have detected clinical and flow cytometric features of immunodeficiency in patients with somatic *GATA2* mutations and myeloid malignancies, indicating that *GATA2* mutations may exert pleiotropic effect on terminal immune lineages that alters immunity even when acquired later in life and may produce a similar immunophenotype as germline mutations [5]. For example, up to 41% of patients with somatic *GATA2* mutations and myelodysplasia developed invasive fungal infections in a prior series [11]. Along the same lines, somatic *GATA2* mutations are theoretically expected to increase the risk for NTM infection similar to germline mutations, yet the currently limited literature cannot support this association. Several NTM species were reported in patients with *GATA2* mutations, but these reports mostly do not elaborate on the type of mutation (Supplementary Table 1). We found only 1 report of a patient with confirmed somatic *GATA2* mutation and probable mycobacterial infection in the setting of MDS [12]. The patient had a hypercellular bone marrow and a trinucleotide *GATA2* deletion c.1168_1170delAAG; p.Lys390del and a co-mutation in *ASXL1*, similar to our patient. Infection was not confirmed by culture. However, the patient improved after empiric mycobacterial treatment.

The conventional method for determining whether *GATA2* mutation is somatic is to perform a skin fibroblast *GATA2* analysis [5]. Mutations not found on skin fibroblasts are acquired after birth [5]. Our patient did not undergo skin testing and so we are unable to fully confirm the nature of his *GATA2* mutations. Nonetheless, given our patient's age at disease onset, we have a strong suspicion that his *GATA2* mutations were somatic.

This is a unique case of disseminated infection with 3 different NTMs in an elderly patient with *GATA2* mutations, likely somatic. This is also the first report of *M simiae* infection in the setting of *GATA2* mutations. Molecular testing was used to confirm identification of the different mycobacterial species. MALDI-TOF MS has been effectively used for the rapid identification of NTMs but still lacks the nuances of identifying *M avium* complex to the species level. Alternatively, 16S rRNA Sanger sequencing is a phylogenetic tool that helps distinguish members within the *avium* complex while adding confidence to the identification of *M avium* and *M simiae*. Unfortunately, disseminated infection in the setting of hematologic malignancy led to a poor outcome in our patient despite aggressive antimicrobial therapy.

Continued research is needed to improve understanding of the complex association/overlap between immunologic deficiencies and NTM infections and their expected outcomes. Clinicians should maintain an index of suspicion for mycobacterial infections in patients with myelodysplasias.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. This report does not include factors necessitating patient consent.

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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.

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