Mediastinal and Disseminated *Mycobacterium kansasii* Disease in GATA2 Deficiency

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Abstract

Rationale: *Mycobacterium kansasii* usually causes chronic pulmonary infections in immunocompetent patients. In contrast, disseminated *M. kansasii* disease is commonly associated with advanced human immunodeficiency virus infection, but is reported infrequently in other immunocompromised patients.

Objectives: To identify common clinical manifestations and potential risk factors for *M. kansasii* infection in patients with GATA2 deficiency.

Methods: We reviewed *M. kansasii* disease associated with GATA2 deficiency at one institution and disease associated with primary and other immunodeficiencies reported in the literature.

Measurements and Main Results: Nine patients with GATA2 deficiency developed *M. kansasii* infections. Six patients developed

disseminated disease. All patients presented with significant mediastinal lymphadenopathy or abscesses. Seven patients had pulmonary risk factors, including six smokers. The majority of patients had low numbers of neutrophils, monocytes, B cells, CD4⁺ T cells, and natural killer cells. Other conditions associated with disseminated *M. kansasii* disease were thymic disorders and IFN- γ /IL-12 defects.

Conclusions: Disseminated *M. kansasii* disease involving mediastinal lymph nodes is surprisingly common in GATA2 deficiency, but also occurs in defects of IFN- γ synthesis and response. Disseminated *M. kansasii* should be considered a marker indicating a need to evaluate for immunodeficiency syndromes.

Keywords: lymphadenopathy; nontuberculous; immunodeficiency; myelodysplasia; mediastinal

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Mycobacterium kansasii is a common cause of nontuberculous mycobacterial (NTM) infections in the United States, second only to *Mycobacterium avium* complex (MAC)

(1). Disseminated *M. kansasii* disease has been reported most commonly in patients with advanced HIV infection (CD4⁺ cell count, <50/ μ l) (1, 2). Disseminated disease

has been reported less frequently in patients with other causes of immunocompromise, including hematologic malignancies, steroid use, and primary immunodeficiency

diseases, such as DiGeorge syndrome, defects in the IFN- γ /IL-12 pathway, and NF- κ B essential modulator (NEMO) deficiency. There also have been reports of disseminated (3, 4) and localized *M. kansasii* infections in GATA2 deficiency (5–8).

The previously described monocytopenia and mycobacterial infection (MonoMAC) syndrome, also known as dendritic cell, monocyte, and B/NK (natural killer) lymphoid (DCML) deficiency, is caused by heterozygous mutations in the GATA2 gene resulting in a loss of function of the GATA2 protein (9, 10). GATA2 is a transcription factor required for the differentiation and proliferation of hematopoietic stem cells (HSCs). Deficiency of GATA2 contributes susceptibility to severe and disseminated viral (e.g., human papillomavirus), fungal, and NTM infections, pulmonary alveolar proteinosis, and myelodysplastic syndrome (MDS) (11). The hematologic profile of patients includes deficiencies of NK cells, monocytes, and B cells, and down-regulation of GATA2 has also been associated with impaired phagocytic activity of alveolar macrophages (12).

Impressed by the frequency of *M. kansasii* infection in patients with GATA2 deficiency seen at the National Institutes of Health (NIH, Bethesda, MD) through 2015, we sought to identify common clinical manifestations and potential risk factors for this infection.

Methods

Study Design

This study was a retrospective cohort study of 75 patients with GATA2 deficiency seen at the NIH between 1992 and 2015. All patients described had provided informed consent on approved protocols of the National Institute of Allergy and Infectious Diseases, National Institutes of Health. Records were searched for immunological profiles, presenting symptoms, microbiological studies, treatments, and outcomes. Disseminated *M. kansasii* infections were defined as the isolation of the pathogen from blood or bone marrow or the documented involvement of two or more noncontiguous tissues. Complete clinical descriptions of patients are provided in the online supplement.

Review of the Literature

A systematic search of all published cases of disseminated *M. kansasii* disease in patients with primary immunodeficiencies was conducted through October 2015. In PubMed, PubMed Central, and Embase, search terms included disseminated, *kansasii*, immunodeficiency, immune, and deficiency. Disseminated disease was defined as stated previously. All cases involving HIV, cancer, or iatrogenic immunodeficiencies were excluded. A total of nine cases meeting our criteria were identified.

Results

Clinical Features

Of 75 patients in our NIH cohort of patients with GATA2 deficiency, we identified 23 patients (31%) with 29 NTM infections: 15 (52%) with MAC, 9 (31%) with *M. kansasii*, 4 (14%) with *Mycobacterium fortuitum*, and 1 (3%) with *Mycobacterium abscessus* infection. The clinical presentations of patients with *M. kansasii* infections are summarized in Table E1 in the online supplement. All nine patients with *M. kansasii* infections presented with mediastinal lymphadenopathy or abscesses (Figure 1). Six of these patients (67%) developed disseminated disease, with five of the disseminated infections involving abdominal or pelvic lymphadenopathy and four involving cutaneous spread.

Seven of the nine patients (78%) had pulmonary risk factors, including six patients with significant tobacco exposure (mean, 7 pack-years; range, 2–10) and one patient with documented prior lung disease. All six patients with disseminated infections had either a significant smoking history or prior lung disease. Both patients without prior pulmonary disease had localized pulmonary infections. Additional risk factors included splenectomy (one patient) and immunosuppressive therapy (one patient). No patients were receiving antibiotic prophylaxis at the time of presentation.

The mean age of *M. kansasii*-related symptom onset for all patients was 31 years (range, 21–51). The mean age of infection for smoking patients was 25 years (range, 21–35) compared with a mean age of 41 years (range, 28–51) for the nonsmoking patients.

Immunological Profiles

Complete blood counts and flow cytometric analyses were available before or during treatment for six of nine patients (four patients with disseminated disease and two with localized infections). Five patients (55%) were neutropenic (mean, 1,180 [1.18K] cells/ μ l; range, 0.36K–3.27K cells/ μ l; normal, 1.61K–6.20K cells/ μ l). Six (67%) were monocytopenic (mean, 0.03K cells/ μ l; range, 0–0.14K cells/ μ l; normal, 0.25K–0.86K cells/ μ l). Six (67%) were lymphocytopenic (mean, 0.31K cells/ μ l; range, 0.01K–0.77K cells/ μ l; normal, 1.11K–3.36K cells/ μ l). Five (55%) had CD4⁺ lymphocytopenia (mean, 276 cells/ μ l; range, 117–549 cells/ μ l; normal, 359–1,514 cells/ μ l). Four (44%) had CD8⁺ lymphocytopenia (mean, 216 cells/ μ l; range, 60–496 cells/ μ l; normal, 181–850 cells/ μ l). Six (67%) had severe NK cell lymphocytopenia (mean, 3 cells/ μ l; range, 0–10 cells/ μ l; normal, 119–692 cells/ μ l). Six (67%) had B-cell lymphocytopenia (mean, 5 cells/ μ l; range, 0–16 cells/ μ l; normal, 58–343 cells/ μ l). Immunological profiles for all patients are summarized in Table E2.

Microbiological Studies

Eight of nine patients had adequate records of microbiological studies. Six of nine patients (67%) had mediastinal lymph node biopsies positive for *M. kansasii* by culture or PCR. Four patients (44%) had positive bronchoalveolar lavage cultures and four patients (44%) had positive skin biopsies.

Treatments and Outcomes

Antimicrobial treatments were adequately documented in all patients. Recurrent infections were reported in four patients (44%), all of whom were smokers with disseminated disease. Two cases of recurrent infections were attributed to medical nonadherence. Both patients without either a smoking history or prior lung disease had complete resolution of their infections. Two patients (one smoker and one nonsmoker) developed subsequent pulmonary MAC infections. All subjects entering into therapy for *M. kansasii* infection improved with antimicrobial therapy, although one patient required immune augmentation with IFN- γ .

GATA2 mutations have been identified in eight of nine patients (89%). GATA2

Figure 1. Axial computed tomographic (CT) images showing mediastinal lymphadenopathy in patients with GATA2 deficiency. (A) Postcontrast CT image showing partially calcified and necrotic, heterogeneously enhancing subcarinal and right hilar lymph node masses (arrows). (B) Contrast CT image showing rim-enhancing lymph node conglomerate in the subclavicular region (arrow). (C) Noncontrast CT image showing partially calcified right parasternal mass (arrow). (D) Postcontrast CT image showing right paratracheal mass with necrotic center (arrow).

deficiency was suspected in the ninth patient (patient 2) given her compatible clinical history, including papillomavirus-related dysplasia, pulmonary alveolar proteinosis, and MDS. Five patients (55%) later developed MDS and two patients (22%) developed metastatic cancer. Overall, three patients (33%) died, but no deaths were attributed directly to progression of *M. kansasii* disease. Three patients (33%) ultimately underwent hematopoietic stem cell transplant (HSCT); none had progression of *M. kansasii* disease and in all cases the *M. kansasii* infection continued to resolve. Patients 3 and 5 underwent HSCT 42 and 15 months after their initial *M. kansasii* diagnoses, respectively; both died shortly after HSCT of complications unrelated to their mycobacterial infections. Patient 6 underwent successful HSCT about 8 months after initial diagnosis of *M. kansasii* disease. His post-transplantation course was complicated by an apparent immune reconstitution in the pleural space, which led to recurrence of a sterile pleural effusion.

Review of the Literature

Review of the literature on disseminated *M. kansasii* identified 11 further cases of disease in patients with primary or

other immunodeficiencies not due to the well-documented associations with HIV or malignancy (see Table E3). These included NEMO deficiency (one patient) (13) and defects in the IFN- γ /IL-12 pathway: IFN- γ receptor deficiency (one patient) (14), IL-12 receptor deficiency (one patient) (15), and autoantibodies to IFN- γ (one patient) (16). Disseminated disease has been reported in a patient with a known GATA2 mutation (3) and a patient whose clinical history is compatible with GATA2 deficiency (4).

Disseminated *M. kansasii* infection was described in a 13-month-old male with complete DiGeorge syndrome (17). We identified three additional reports of disseminated disease in patients diagnosed with thymic dysplasia (18, 19) or alymphoplasia (20), and an additional report in a patient with severe combined immunodeficiency (SCID) who was found to have a rudimentary thymus *post mortem* (21). Four of the five patients with thymic abnormalities developed disseminated disease with osteomyelitis before 3 years of age, and three patients died on progression of their infections. On the basis of published clinical histories documenting immunoglobulin deficiencies and present but dysplastic thymi, it is

possible that past cases classified as thymic dysplasia or alymphoplasia were due to SCID or partial DiGeorge syndrome.

Discussion

Before the advent of highly active antiretroviral therapy (HAART), disseminated *M. kansasii* disease was considered an AIDS-defining illness, with incidences ranging from 0.14 to 0.44% (22–24). A review of 41,439 cases of AIDS in United States during the pre-HAART era identified 2,269 (5.5%) disseminated NTM infections in patients with AIDS, with 1,906 (84%) of those due to MAC and only 57 (2.5%) due to *M. kansasii* infections (23). Since the introduction of HAART, disseminated disease is reported less frequently, although dissemination continues to occur in patients with severe HIV-associated T-cell lymphocytopenia (25, 26).

In a literature review of non-HIV patients with disseminated *M. kansasii* infections, Han and colleagues identified 63 patients with risk factors classified in 76.2% of patients, most commonly hematologic malignancy and steroid use

(27). They identified primary immunodeficiency in just three patients: SCID, primary lymphopenic immunodeficiency, and thymic aplasia and dysgammaglobulinemia. Reviews of infectious complications in patients with hairy cell leukemia have estimated the incidence of disseminated *M. kansasii* infection as between 3.2 and 7.9% (28–30). Disseminated disease has been reported less frequently in other types of leukemia, including chronic myelogenous leukemia (31, 32) and acute myelogenous leukemia (32), with overall incidences estimated at 2 cases per 100,000 patients with cancer (33). Other conditions associated infrequently with disseminated *M. kansasii* disease include solid cancers, solid organ transplantation, and HSCT (32).

Compared with disseminated infection in other immunocompromised populations, GATA2-deficient patients predominantly present with significant mediastinal lymphadenopathy without bony involvement. Disseminated disease in DiGeorge syndrome or in patients with thymic dysplasia/lymphoplasia typically occurs in infancy. The presentation of disseminated disease in early childhood in patients with thymic aplasia/dysplasia indicates the importance of cellular immunity in the control of *M. kansasii*. In contrast, patients with GATA2 deficiency develop disseminated disease beginning in their early 20s. The levels of B, NK, and CD4⁺ T cells, and of monocytes, are

variable in GATA2 deficiency; however, infectious complications increase as cytopenias evolve, which typically begins in late adolescence or adulthood (11). The absence of disseminated *M. kansasii* disease in childhood likely results from intact T-cell and monocyte compartments in GATA2 deficiency early in life.

Intact macrophage phagocytosis and subsequent IFN- γ /IL-12 signaling are critical for the host defense against NTM. Preexisting lung disease (e.g., heavy smoking, chronic obstructive pulmonary disease) is the most prevalent underlying condition among patients with pulmonary *M. kansasii* infections (34). Underlying lung conditions likely increase susceptibility to infection due to impaired alveolar macrophage phagocytic activity (35) and immune responses (36). However, the lack of association between underlying lung disease alone and disseminated *M. kansasii* disease (34) suggests that extrapulmonary immune responses largely remain intact in these patients. Conversely, the history of smoking in the majority of GATA2-deficient patients with disseminated disease suggests that in the setting of primary immune defects, extensive tobacco exposure may increase the risk for *M. kansasii* dissemination. The active smoking rate is approximately 15% in our adult GATA2 cohort, comparable to an estimated 18% active rate of smoking in all U.S. adults (37). However, the overall ever-smoking rate (including former smokers) is

approximately 29% in our adult GATA2 cohort. We hypothesize that the known effect of smoking on alveolar macrophages may be markedly accentuated in patients with primary monocyte/macrophage dysfunction, such as GATA2 deficiency, increasing the risk of disseminated disease (12).

Disseminated *M. kansasii* disease is a rare complication seen in a limited number of immunodeficiency conditions. Our cohort of GATA2-deficient patients has a higher incidence of *M. kansasii* infection (12%) and disseminated disease (8%) than for any previously reported immune diseases. Two additional cases of disseminated disease (3, 4) and four cases of localized *M. kansasii* infections in patients with GATA2 deficiency have already been reported (5–8). Given this frequency, macrolide prophylaxis seems prudent; we have not detected any *M. kansasii* infections among patients receiving prophylactic azithromycin. Like other NTM infections, disseminated *M. kansasii* disease appears to be more commonly associated with immunodeficiency, especially GATA2 deficiency and other defects of lymphoid or IFN- γ /IL-12 immunity. Patients who present with *M. kansasii* mediastinal lymphadenopathy or abscess should be investigated for GATA2 deficiency. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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