

Interferon- γ Autoantibodies as Predisposing Factor for Nontuberculous Mycobacterial Infection

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DOI: <http://dx.doi.org/10.3201/eid2206.151860>

To the Editor: Recent advances in the understanding of antimycobacterial immune response have led to descriptions of predisposing conditions to dissemination of nontuberculous mycobacteria (NTM) infection. The interferon-gamma (IFN- γ)/interleukin-12 (IL-12) axis is a critical pathway for intracellular killing of mycobacteria (online Technical Appendix Figure, <http://wwwnc.cdc.gov/EID/article/22/6/15-1860-Techapp.pdf>) (1). We report a case of disseminated NTM infection in a woman from Laos who showed IFN- γ autoantibodies. We also conducted a literature review to review similar cases.

A previously healthy 50-year-old woman from Laos was referred to Hospices Civils de Lyon, France, for fever and generalized lymphadenopathies; pathological examination revealed a nonnecrotizing granuloma. Culture yielded *Mycobacterium fortuitum*. After a 3-month azithromycin/ciprofloxacin regimen, symptoms resolved. A few months later, a computed tomography scan showed persistence of enlarged mediastinal lymph nodes; biopsy disclosed nonspecific sinus histiocytosis. Mycobacterial cultures were negative. One month later, the patient reported intense dorsal spine pain. She was diagnosed with multifocal vertebral osteomyelitis, and tissue specimens tested positive for *M. intracellulare*. Azithromycin/ciprofloxacin was prescribed again. At 6 months, lesions worsened, and epidural abscess led to spinal cord compression, requiring decompressive laminectomy. Postoperative cultures were positive for *M. intracellulare*. Treatment was changed to azithromycin, rifabutin, ethambutol, and amikacin for 2 weeks, then rifabutin and moxifloxacin, which led to clinical improvement.

The patient experienced 2 episodes of thoracic herpes zoster concomitantly to each episode of illness. The recurrent NTM infection led us to investigate her immune status. Results of standard immunologic tests (leukocyte, serum level of immunoglobulin isotypes, and T-, B-, and NK cell counts) and in vitro T-cell proliferation were normal; HIV testing was negative. Given its critical role in *Mycobacteria* clearance by host cells, we used IFN- γ whole-blood activation to investigate further. IFN- γ plasma level was undetectable, excluding complete forms of IFN- γ R1/R2. IL-12 p40 subunit plasmatic level was decreased, but the IL-12 receptor was present and functional. In addition, both BCG and IL-12 stimulations failed to trigger IFN- γ production. Ultimately, the detection of IFN- γ autoantibodies in high levels explained these abnormalities. Antimycobacterial treatment was continued for 2 years, then changed to azithromycin suppressive therapy; IFN- γ autoantibodies remained positive at the time of this report, 2 years after azithromycin initiation.

We reviewed the literature and found 63 other cases of IFN- γ autoantibody-related NTM infection with sufficient detail to provide clinically relevant material for optimizing disease management (Table; online Technical Appendix). These cases overwhelmingly occurred among Asian populations (92.2%) (2). Disease incidence may be underestimated, as suggested by large studies describing Asian patients with disseminated NTM infection without evidence of impaired immunity but for whom the IL-12/IFN- γ axis was not investigated (3). This acquired autoantibodies-mediated immunodeficiency is more frequent among women, in whom the disease typically manifests in the second half of adult life (median 48 [IQR 44.8–60.0] years of age). Reported female:male sex ratios are 23/36 in Asian-born ($n = 59$) and 4/1 in non-Asian ($n = 5$) case-patients, respectively. Mechanism of the disease is briefly discussed in the online Technical Appendix.

M. avium complex predominated in the literature review, accounting for 40.4% of cases, followed by *M. abscessus* (31.6%) and *M. fortuitum* (12.3%). Infections were mostly multifocal, affecting lymph nodes ($n = 51$, 79.7%), osteoarticular tissue ($n = 37$, 57.8%), lungs ($n = 30$, 46.9%), and skin and/or soft tissues ($n = 24$, 37.5%). Aside from NTM infections, other opportunistic infections were reported in 39 (75.0%) patients, mostly *Herpesviridae* reactivations (44.2%) and *Salmonella* infections (25.0%) (3–6).

Specific treatment for IFN- γ autoantibodies-associated NTM infection is not codified and required prolonged, multiple-drug regimens. The median treatment duration for the studies we reviewed was 31 (IQR 22.8–60.0) months. In some studies, clinicians used IFN- γ administration (5 patients, 1 of whom was cured), but treatment likely was invalidated by the autoimmune-driven inhibitory

Table. Summary of clinically relevant characteristics of 64 case-patients with IFN- γ autoantibody-related nontuberculous mycobacterial infection found in literature review*

Characteristics	Value
Demographics	
Female sex	40 (62.5)
Median age, y (IQR)	48.0 (44.8–60.0)
Asian origin	59 (92.2)
Other autoimmune diseases	7/27 (25.9)
Etiologic agents	
<i>Mycobacterium avium</i>	23 (40.4)
<i>M. abscessus</i>	18 (31.6)
<i>M. fortuitum</i>	7 (12.3)
<i>M. tuberculosis</i>	6 (10.5)
Other opportunistic infections	39/52 (75.0)
<i>Herpesviridae</i> reactivations	23/52 (44.2)
<i>Salmonella</i> spp.	13/52 (25.0)
Median duration of intensive-phase therapy, mo (IQR)	31.0 (22.8–60.0)
≥6	31/31 (100)
≥12	29/31 (93.5)
≥18	27/31 (87.1)
≥24	23/31 (74.2)
Long-term antimicrobial suppressive therapy	3/30 (10.0)
Immunomodulatory therapies	10/30 (33.3)
Rituximab	6/30 (20.0)
IFN- γ	5/30 (16.7)
Intravenous immunoglobulins	2/30 (6.7)
Plasmapheresis	2/30 (6.7)
Cyclophosphamid	1/30 (3.3)
Outcome	
Cure	21/62 (33.9)
Improvement	6/62 (9.7)
Relapse/persistence	29/62 (46.8)
Death	6/62 (9.7)

*Values are no. (%) except as indicated. Only articles with sufficient detail were analyzed. A complete listing of articles reviewed from the literature is provided in the online Technical Appendix Table (<http://wwwnc.cdc.gov/EID/article/22/6/15-1860-Techapp1.pdf>). IQR, interquartile range; IFN- γ , interferon gamma.

†Denominators indicate number of case-patients for which category of data was available.

activity (5,2,7). Other strategies included intravenous immunoglobulin (n = 2), plasmapheresis (n = 2), and cyclophosphamide (n = 1) (7–9). The use of rituximab, a chimeric anti-CD20 monoclonal antibody targeting B-cells, has been recently associated with clinical response and decrease in IFN- γ autoantibody levels as well as neutralizing ability (6,7).

Final outcome was available for 56 patients who completed the intensive treatment phase; 21 (37.5%) were declared cured. Six (10.7%) patients died, and 29 (51.8%) had persistent or relapsing infections. At the time of this report, additional patients were still being treated and showed improvement of symptoms. Despite this high rate of failure, long-term antimicrobial drug suppressive therapy has rarely been proposed as a causal factor. The origin of the case we report was related to the use of azithromycin suppressive therapy, similarly to disseminated NTM disease prophylaxis in HIV-infected patients before the era of highly active antiretroviral therapies (10), assuming the risk/

benefit balance including the possibility of NTM macrolide-resistant strain selection.

IFN- γ autoantibodies are evidence of acquired immunodeficiency that should be considered in cases of unexplained disseminated NTM infections in Asian-born persons. Use of immunomodulation strategies is still debated, and long-term suppressive treatment should be considered for persisting high levels of neutralizing antibodies.

Acknowledgments

We thank Lyon tuberculosis study group members F. Ader, F. Biron, A. Boibieux, A. Bouaziz, E. Braun, G. Catho, N. Charhon, C. Chidiac, W. Chumbi-Flores, S. Couraud, G. Devouassoux, O. Dumitrescu, S. Ernesto, T. Ferry, D. Floret, N. Freymond, S. Gardes, S. Gerbier-Colomban, Y. Gillet, S. Goutelle, J. Grando, R. Grima, L. Hees, J. Karsenty, L. Kiakouama-Maleka, G. Lina, J. M. Maury, P. Miaillhes, P. Nesme, T. Perpoint, E. Perrot, A. S. Ronnaux-Baron, S. Roux, J. Saison, A. Senechal, P. J. Souquet, H. Thai Van, F. Tronc, F. Valour, and P. Vanhems for choosing research field priorities and editing one another's reports for this article.

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Loss of 89K Pathogenicity Island in Epidemic *Streptococcus suis*, China

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DOI: <http://dx.doi.org/10.32032/eid2206.152010>

To the Editor: *Streptococcus suis* serotype 2 (SS2) is a previously neglected, newly emerging human pathogen that causes occupational and opportunistic infections (1,2). Outbreaks of fatal human SS2 infections in China, featuring streptococcal toxic shock syndrome, in 2005 seriously challenged global public health (3–5). The epidemic strain is unusual in that it contains a unique 89-kb (89K) pathogenicity island (PAI) (3,6,7). We observed the loss of genes from the 89K PAI in sporadic cases in southern China in 2007, implying the dynamic evolution of this PAI (8). Therefore, 89K PAI might be able to be used to monitor prevalent strains of *S. suis* in China (8).

We report 10 recurrent cases of human *S. suis* infections during 2008–2015 in southern China. Most of the hospitalized patients were male workers in close contact with pigs, pork products, or both. These patients typically exhibited clinical syndromes of meningitis, including headache, coma, vomiting, and fever. The bacterial strains acquired from humans were as follows: 2 isolates in 2008 (Stre08001 and Stre08002), 2 in 2009 (Stre09001 and Stre09002), 2 in 2011 (Stre11001 and Stre11002), 3 in 2013 (Stre13002,

Stre13003, and Stre13004), and 1 in 2015 (Stre15001). Microbial and molecular assays proved that these clinical isolates were *S. suis* (online Technical Appendix Figures 1, 2, <http://wwwnc.cdc.gov/EID/article/22/6/15-2010-Techapp1.pdf>). Multiplex PCR-based molecular determination (*16S rDNA*, *mrp*, *epf*, and *cps-2j*) suggested that all strains except Stre13002 were SS2 (online Technical Appendix Figure 2) (3). To determine whether these clinical isolates derived from the same Chinese epidemic clone 05ZYH33, we sequenced an array of virulence factor-encoding genes, as well as the *16S rDNA* genes. Phylogenetic trees indicated that all 10 clinical strains are classified into the same subclade as that of the strain 05ZYH33 (online Technical Appendix Figure 2).

Subsequent analyses by pulsed-field gel electrophoresis revealed that genotypes are diverse among these clinical strains, which can be roughly divided into 6 groups (online Technical Appendix Figure 3). Given that the Sao surface antigen protein possesses 3 allelic variants (Sao-L [670 aa], Sao-M [580 aa], and Sao-S [489/490 aa]) (9), we thus assayed it with these clinical strains. Unexpectedly, we found 2 more new allelic variants, referred to as Sao-L1 (640 aa) and Sao-L2 (611 aa). Except for the strain BM407, which is a Chinese epidemic SS2 encoding Sao-L1, a version 30 residues shorter than Sao-L, 8 of the 10 clinical *S. suis* isolates consistently had the same new form of Sao protein, Sao-L2 (611 aa) (online Technical Appendix Figure 4).

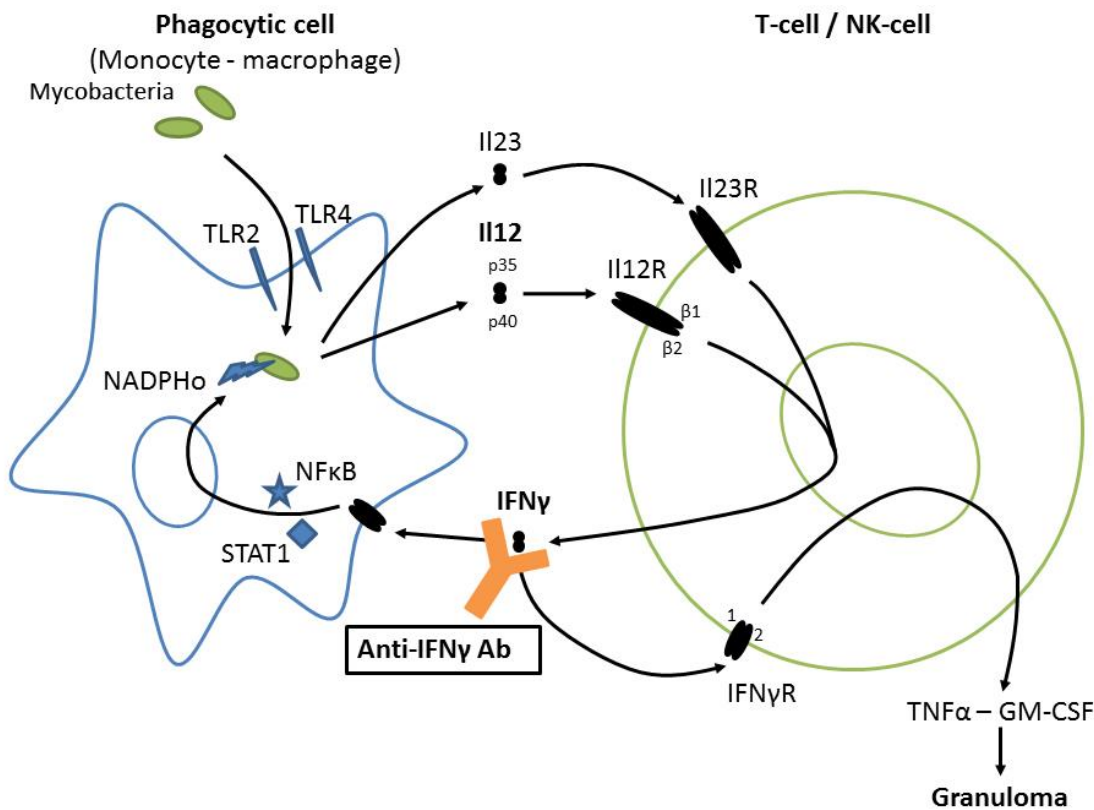
Because 89K PAI is in dynamic evolution, determining whether it remains present in clinical strains is of interest. As previously designed (online Technical Appendix Table 1), a specific pair of boundary primers (1/6) was applied for PCR-based detection of the 89K PAI (Figure, panel A, <http://wwwnc.cdc.gov/EID/article/22/6/15-2010-F1.htm>). In principle, the PCR-positive result suggests the absence of 89K PAI, whereas the PCR-negative result indicates the presence of 89K PAI (6,8). Unlike the epidemic strain 05ZYH33 that has the 89K PAI, 9 of the 10 clinical strains examined (Stre08001, Stre08002, Stre09001, Stre09002, Stre11001, Stre11002, Stre13002, Stre13003, and Stre13004) were unexpectedly found to be PCR positive for the unique 1/6 DNA fragment with expected size of ≈ 1.5 kb (Figure, panel B). This finding indicates that the 89K PAI is lost in these 9 clinical strains. We saw similar scenarios in the subsequent PCRs for other inner genes/DNA fragments (943 and 944 [10]; 1/2, 3/4, and 5/6 [8]) inside of 89K PAI (Figure, panel C). Further DNA sequencing of the 1/6 PCR product showed that it matches well with the 2 boundary regions neighboring the 89K PAI, validating the loss of 89K PAI in these 9 clinical isolates (Figure, panel D). In contrast, the strain Stre15001 behaved similarly to that of the 05ZYH33 containing the 89K PAI, in that both are PCR positive for the 4 amplicons

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Technical Appendix

The mechanism of disease for nontuberculous mycobacterial infection is not completely understood, but 3 likely components include 1) genetics, because a strong association with HLA-Dr β 1602 and HLA-Dr β 0502 was demonstrated among 17 patients, but without familial clustering (1); 2) impaired immune signaling leading to autoantibody production; and 3) environmental factors, possibly taking place during childhood, considering that most studied case-patients are Asian-born.



Technical Appendix Figure. The interferon-gamma (IFN- γ)/interleukine-12 (IL-12) axis as a critical pathway for intracellular killing of mycobacteria.

Technical Appendix Table. Published cases of non-tuberculous mycobacterial infection caused by interferon- γ autoantibodies, 2004–2015*

Case-patient sex, age (y)	Origin	Baseline treatment regimen	Duration (months)	Immune therapies	Outcome	Reference
M, 47	Philippines	AMK, CAM, EB, INH, PZA, doxycyline	NA	IFN γ	Died	Doffinger et al., 2004 (2)
F, 25	Thailand	NA	NA	None	Died	Hoflich et al., 2004 (3)
F, 46	United Kingdom	CFZ, EB, CAM, RIB	42	IFN γ	Cured	Kampmann et al., 2005 (4)
M, 32	South Africa	EB, CAM, RIB	NA	None	Cured	(4)
F, 59	United Kingdom	NA	NA	None	Cured	(4)
F, 43	Taiwan	NA	60	None	Cured	Patel et al., 2005 (5)
F, 52	China	NA	> 60	None	Persistent infection	(5)
F, 40	Philippines	NA	> 60	None	Persistent infection	(5)
F, 31	Philippines	NA	> 30	None	Persistent infection	(5)
F, 46	Philippines	CAM, EB, INH, LNZ, MFL, TIG	> 60	IFN- γ , rituximab	Relapse	(5)
F, 69	Philippines	AMK, AMX/CLV, AZI, CFZ, EB, INH, LNZ, MER, RMP, TIG	> 84	IFN- γ , Ivlg, plasmapheresis, rituximab	Relapse	Browne et al., 2012 (6)
M, 54	Japan	CAM, EB, RMP, SM	NA	None	Cured	Tanaka, 2007 (7)
F, 38	Philippines	AZI, EB, RIB	Under treatment	Cyclophosphamide, plasmapheresis	Improved	Baerlecken et al., 2009 (8)
F, 44	Japan	CAM, EB, MFL, RMP, SM	> 18	Ivlg	Cured	Koya et al., 2009 (9)
M, 56	Thailand	EB, INH, MFL, PZA, RMP	24	None	Relapse	Kampitak et al., 2011 (10)
M, 45	Thailand	EB, INH, PZA, RMP	Under treatment	None	Improved	(10)
M, 39	Thailand	EB, INH, MFL, PZA, RMP	Under treatment	None	Improved	(10)
F, 50	Laos	CAM, EB, MFL	> 12	IFN- γ , rituximab	Relapse	(6)
F, 60	Laos	AMK, AZI/CAM, EB, INH, LFL/MFL, PZA, RMP	12	Rituximab	Cured	(6)
F, 45	Thailand	AMK, CAM, EB	8	None	Cured	Picque et al., 2012 (11)
F, 40	Thailand	AZI/CAM, EB, LFL, RMP	Under treatment	None	Improved	Chaisathaphol et al., 2013 (12)
M, 50	China	NA	NA	NA	Cured	Chi et al., 2013 (1)
F, 47	China	NA	NA	NA	Persistent infection	(1)
M, 69	China	NA	NA	NA	Persistent infection	(1)
F, 47	China	NA	NA	NA	Persistent infection	(1)
M, 55	China	NA	NA	NA	Cured	(1)
M, 81	China	NA	NA	NA	Persistent infection	(1)
M, 61	China	NA	NA	NA	Cured	(1)
M, 84	China	NA	NA	NA	Cured	(1)
M, 44	China	NA	NA	NA	Cured	(1)
F, 59	China	NA	NA	NA	Persistent infection	(1)
M, 48	China	NA	NA	NA	Persistent infection	(1)
F, 48	China	NA	NA	NA	Persistent infection	(1)
F, 45	China	NA	NA	NA	Persistent infection	(1)
F, 72	China	NA	NA	NA	Died	(1)
F, 47	China	NA	NA	NA	NA	(1)
F, 47	China	NA	NA	NA	Persistent infection	(1)

Case-patient sex, age (y)	Origin	Baseline treatment regimen	Duration (months)	Immune therapies	Outcome	Reference
M, 60	China	NA	NA	NA	Persistent infection	(1)
M, 78	Japan	AZI, IMI, MFL, TM	NA	Rituximab	Relapse	Czaja et al., 2013 (13)
M, 66	Japan	AMK, CAM, EB, LVF, RMP	NA	None	Cured	Ishii et al., 2013 (14)
M, 53	Japan	EB, INH, RMP	NA	None	Died	Nei et al., 2013 (15)
F, 49	Laos	CAM, EB, RMP	NA	None	Died	Poulin et al., 2013 (16)
F, 64	Japan	CAM, EB, RFP	NA	None	NA	Yamaguchi et al., 2013 (17)
F, 47	Asia	Included LNZ	8.5	NA	Relapse	Chetchotisakd et al., 2014 (18)
M, 61	Asia	Included LNZ	35.5	NA	Cured	Browne et al., 2012 (19)
F, 15	Asia	Included LNZ	31	NA	Cured	(19)
F, 47	Asia	Included LNZ	24.5	NA	Relapse	(19)
M, 48	Asia	Included LNZ	25	NA	Persistent infection	(19)
F, 45	Asia	Included LNZ	126	NA	Relapse	(19)
F, 43	Asia	Included LNZ	59	NA	Relapse	(19)
F, 42	Asia	Included LNZ	49	NA	Died	(19)
F, 47	Asia	Included LNZ	104.5	NA	Cured	(19)
F, 45	Asia	Included LNZ	24	NA	Persistent infection	(19)
F, 57	Asia	Included LNZ	75.5	NA	Persistent infection	(19)
F, 48	Asia	Included LNZ	76	NA	Persistent infection	(19)
M, 63	Asia	Included LNZ	18.5	NA	Cured	(19)
M, 34	Asia	Included LNZ	33.5	NA	Persistent infection	(19)
F, 34	Asia	Included LNZ	21.5	NA	Cured	(19)
F, 39	United States	AZI, EB, LFL, RMP	Under treatment	None	Improved	O'Connell et al., 2014 (20)
F, 65	Germany	CAM, EMB, RMP	18	Rituximab	Persistent infection	Hanitsch et al., 2015 (21)
M, 65	Japan	CAM, EMB, RMP	36	NA	Cured	Hase et al., 2015 (22)
F, 65	Japan	CAM, EMB, KAN/LVX, RMP	24	NA	Relapse	Nishimura et al., 2015 (23)
M, 71	Cambodia	CAM, CIP, RMP	Under treatment	None	Improved	Otome et al., 2015 (24)
F, 50	Laos	AMK, AZI, EB, MFL, RIB	24	None	Cured	Present case

*AMK, amikacin; CAM, clarithromycin; EB, ethambutol; INH, isoniazide; PZA, pyrazinamide; NA, data not available; IFN γ , interferon gamma; CFZ, clofazimine; RIB, rifabutin; LNZ, linezolid; MFL, moxifloxacin; TIG, tigecyclin; INH, isoniazide; AMX/CLV, amoxicillin/clavulanate; AZI, azithromycin; CFX, ciprofloxacin; MER, meropenem; RMP, rifampin; Ivlg, intravenous immunoglobulins; SM, streptomycin; AZI, azithromycin; LFL, levofloxacin; IMI, imipenem; TM, tobramycin; LFL, levofloxacin; EMB, ethambutol; KAN, kanamycin; LVX, levofloxacin; CIP, ciprofloxacin.

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