Disseminated Mycobacterium avium Complex Infection in Patients with Autoantibody to Interferon-gamma

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ABSTRACT

Mycobacterium avium complex (MAC) is known as one of common opportunistic infection in advanced AIDS patient. Other immunodeficiency syndromes, especially in helper T-cell, interferon (IFN)-γ, interleukin (IL)-12 pathways are also risk for MAC and intracellular organism infection. Autoantibody to interferon-gamma has been increasingly reported and most cases are Asian population. The clinical presentation from several case series demonstrated severe disseminated MAC infection, sometimes co-infected with other organisms such as non-Typhi Salmonella and rapidly growing mycobacteria. The combination of antimycobacterial agents is a mainstay of treatment. Immunosuppressive or immunomodulatory agents as adjunctive therapy for prevention of relapsed disease should be further studied to optimize the outcome. (J Infect Dis Antimicrob Agents 2013;30:101-7.)

INTRODUCTION

Disseminated Mycobacterium avium complex (MAC) infection is commonly known as opportunistic infection in advanced HIV infected patient, or other less frequently condition such as immunosuppressive therapy, hereditary or acquired T-cell deficiency.1,2 Important immunity against non-tuberculous mycobacterial (NTM) infection including MAC is T helper-1 lymphocyte, cytokines such as interferon (IFN)-γ and interleukin (IL)-12, and macrophage.2,3 Several patients with unexplained non-tuberculous mycobacterial infection were found to have autoantibody to IFN-γ which is susceptible to intracellular pathogen infections.4,5 From the latest case series published in 20116, there were reported 16 patients who had autoantibody to IFN-γ with disseminated NTM infection, and MAC were most frequently found as infective or co-infective pathogen in 9 of 16 patients. In March 2012, we found a patient presented with recurrent Salmonella group D bacteremia and disseminated MAC infection which caused mycobacteremia, left sternoclavicular arthritis, and bone marrow involvement. The infection was responded to standard antimicrobial agents for MAC infection.

Microbiology

Mycobacterium avium complex (MAC), one of slowly growing mycobacteria, are common in many environmental sites including water, soil, and animals.7 By classical definition, MAC comprises of 2 taxa M. avium and M. intracellulare. Nevertheless,
the taxonomy now became complicated, currently; the new species of M. avium has been proposed i.e. susp. avium, susp. silvaticum, and susp. paratuberculosis. Their colonies are heterogeneous morphology and slow growth. For mycobacterial identification, molecular method can accelerate the accuracy of diagnosis. Several novel molecular assays such as real time-PCR and reverse hybridization have proved usefulness for reducing the delay of mycobacterial diagnosis. Innogenetics/ Auto-LiPA 48 can identify several species of mycobacteria including tuberculosis from colonies grew on liquid or solid media.8

**Diagnosis: Autoantibody to interferon-gamma**

Interleukin-12 and interferon-gamma (IL-12-IFN-γ) regulation plays a major role in combat with MAC infections.2 IFN-γ, secreted by activated Th1 cell, is a signal for positive feedback to both macrophages and CD4+ T-cells to eradicate intracellular microorganism.10 Some studies demonstrated autoantibody to IFN-γ has associated with disseminated NTM infection especially in Asian populations.4-6,11-17

The principle method of immunological investigation for IL-12-IFN-γ pathway defect are composed of quantitative lymphocyte subpopulation test, lymphocyte proliferation assays, phagocytic killing activity, testing for IFN-γ receptor, IL-12 receptor and neutralizing autoantibody to interferon-gamma. Quantitative lymphocyte subpopulation test is mainly used to quantify CD4 and CD8 count by flow cytometry, whereas CD19 and CD56 count are subsequently measured.6 Lymphocyte proliferation assay is commonly tested by phytohemagglutinin (PHA) stimulated peripheral blood mononuclear cell (PBMC) response.4-6,11,15 Phytohemagglutinin is a lymphocyte mitogen for stimulation of lymphoblast proliferation which the DNA by products is detectable with qualitative spectrometry. The normal result of PHA stimulation test reveals only lymphocyte proliferative functions. Phagocytic killing activity is generally determined by dihydrorhodamine (DHR) assay which is a screening test for chronic granulomatous disease.6 Meanwhile, the assay used for detecting IFN-γ receptor and IL-12 receptor on monocyte is performed by flow cytometry. The condition of autoantibody to IFN-γ should be suspected when all of aforementioned test results were normal. Enzyme-linked immunosorbent assay (ELISA) is the important technique used for detection of the neutralizing antibody. To detect autoantibody level, the neutralized binding assay is carried out to compare IFN-γ level between patient’s plasma and donor normal plasma in various concentrations. A recombinant human IFN-γ was added to both patient and normal plasma at various concentrations, and IFN-γ concentration was then determined by ELISA. The patient’s IFN-γ level will be decreased at any higher plasma concentration due to neutralizing antibody, but not with the normal donor plasma.11

**Clinical presentation**

Before the advent of AIDS, the most common presentation of MAC infection is different pulmonary diseases e.g. upper lobe fibrocavitary or tuberculosis-like infection, nodular bronchiectasis, solitary nodules, etc., those have been commonly found in non-immunocompromised person.18 Other syndromes are cervical lymphadenitis and disseminated disease which usually occurred in patients with advanced HIV infection.19 MAC is the most common NTM infection involving HIV infected patient whose CD4 count are usually less than 100 cell/mm3.20-21 The organism is an intracellular
organism that preferably infect into circulating monocyte.\textsuperscript{2} However, disseminated MAC infection is uncommon in non-HIV patient.

A series of 129 non HIV infected Thai patients who were diagnosed disseminated NTM infection\textsuperscript{22}, only 12\% of patients had underlying diseases such as diabetes mellitus, malignancy and thalassemia. 81\% and 46\% of patients lived in the northeast of Thailand and worked in farmland, respectively. The most affected organs were lymph node (89\%), skin and soft tissue (26\%), lung (19\%), bone and joint (16\%), blood (15\%), and spleen (9\%), consecutively. 62\% of patients was co-infected with other pathogens which non-Typhi \textit{Salmonella} was the most common (39.5\%).\textsuperscript{22}

Preexisting reactive skin diseases also associated with disseminated NTM infections which were Sweet’s syndrome (70\%), pustular psoriasis (7\%), acute generalized exanthematous pustulosis or AGEP (6\%) and erythema nodosum (5\%). Rapidly growing mycobacteria (75\% of patients) were predominant organism in the study.\textsuperscript{22} None had conditions associated with acquired immunodeficiency such as receipt of steroid or immunosuppressive agents, advance cancer, malnutrition, radiotherapy, or chronic renal disease.

In our knowl edge, there are 13 reported cases of disseminated MAC infection coexisting with laboratory-proven autoantibody to IFN-\(\gamma\) (Table 1).\textsuperscript{6,17} All patients were adult who the age ranged from 31 to 66 years. Nine patients were female and four patients were male. Eleven patients (84\%) were Asian (5 Japanese, 4 Filipino, 1 Taiwanese and 1 Thai) and other 2 patients were English and South African. The infected sites were commonly found in soft tissue, lymph node, lung and musculoskeletal system. All of patients were survived after receiving appropriate antimicrobial regimens; however, some patients had relapse or persistent infection. A review of 6 cases in 2005 identified all patients required long term anti-mycobacterial regimen or prophylaxis.\textsuperscript{5} Five patients had persistent infection whereas the infection was controllable by secondary prophylaxis in one patient.

\textbf{Treatment}

Both specific treatment for opportunistic infection and immunological therapy for auto-antibody are mandatory for this condition. The majority for MAC treatment was extrapolated from HIV-infected patients. The recommended regimen for initial treatment of MAC disease consists of two or more antimycobacterial drugs, which clarithromycin and ethambutol are the two mainstay agents. Rifabutin should be the third drug for severe disease especially in HIV-infected patients, whereas the fourth drug might include injectable agent such as amikacin or streptomycin.\textsuperscript{23} Fluoroquinolones is also alternative agents for disseminated MAC treatment.\textsuperscript{19} Rifampicin had evidence for using as standard combination antibiotics for MAC lung disease with favorable microbiologic response.\textsuperscript{24} Azithromycin was an alternative for clarithromycin in case of disseminated MAC infection in AIDS patients.\textsuperscript{25}

Duration of treatment in HIV-infected patient should be completed a course of \(\geq 12\) month, remain asymptomatic, and have a sustained increase \(\geq 6\) months in their CD4 count to \(> 100\) cell/\(\mu\)L after ART.\textsuperscript{23} Nevertheless, there is no definite duration for MAC treatment in patients who have autoantibody to IFN-\(\gamma\), but they should be received chronic maintenance therapy until the resolution of immunosuppressive state. Reintroduction of antimycobacterial drugs might be necessary when the disease was relapsed.
Treatment of IFN-γ autoantibody had not well established now. Reported adjunctive treatment modalities are summarized in Table 2. Recently, anti CD-20 or rituximab was used as an adjunctive treatment for relapsed and poorly responsive disseminated NTM infection associated with IFN-γ autoantibody\(^\text{26}\). Browne SK et al, 2012 reported 4 patients who were received rituximab ranged between 8-12 doses in the first year as an adjunctive therapy for refractory disease.\(^\text{26}\) After rituximab therapy, the outcomes were improved by clearance of infection and reduction of both inflammatory markers and IFN-γ autoantibody levels. However, recurrence of disease was commonly found, subsequent additional doses were required.

Intravenous immunoglobulin (IVIG)\(^\text{11}\), plasma-

### Table 1. Reported cases of disseminated MAC infection coexisting with laboratory-proven autoantibody to IFN-γ.

<table>
<thead>
<tr>
<th>Patients(^\text{a})</th>
<th>Sex/age</th>
<th>Ethnicity</th>
<th>Organ involvement</th>
<th>Co-infection</th>
<th>Treatment(^\text{a})</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female/46</td>
<td>English</td>
<td>Soft tissue, bone, joint</td>
<td>-</td>
<td>Rifabutin, clofazimine, EC, IFN-γ</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>Male/32</td>
<td>South African</td>
<td>Soft tissue, spine</td>
<td>-</td>
<td>Rifabutin, EC</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>Female/43</td>
<td>Taiwanese</td>
<td>Bone, skin, soft tissue</td>
<td>-</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>Female/45</td>
<td>Filipino</td>
<td>Lymph node, lung, skin</td>
<td>M. chelonae</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>Female/40</td>
<td>Filipino</td>
<td>Lymph node, lung</td>
<td>M. fortuitum, M. abscessus</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>Female/66</td>
<td>Filipino</td>
<td>Lymph node, lung</td>
<td>M. abscessus, P. aeruginosa, Enterococcus spp., and Achromobacter spp.</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>Female/31</td>
<td>Filipino</td>
<td>Appendix, bone, soft tissue, retropharynx</td>
<td>Varicella-Zoster virus</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>Male/54</td>
<td>Japanese</td>
<td>Lymph nodes, bone, lung, stomach, bone marrow, pleura</td>
<td>S. pyogenes</td>
<td>Ampicillin-subbactam, RECS</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>Female/44</td>
<td>Japanese</td>
<td>Bone, soft tissue</td>
<td>-</td>
<td>RECSM</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>Male/66</td>
<td>Japanese</td>
<td>Blood, lung, muscle, bone</td>
<td>-</td>
<td>RECLA, drainage</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>Female/44</td>
<td>Japanese</td>
<td>Bone, soft tissue</td>
<td>-</td>
<td>RECLS, drainage</td>
<td>Survived</td>
</tr>
<tr>
<td>12</td>
<td>Male/54</td>
<td>Japanese</td>
<td>Lymph nodes, spleen, pleura, bone</td>
<td>-</td>
<td>RECS</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>Female/40</td>
<td>Thai</td>
<td>Blood, bone marrow, joint</td>
<td>Salmonella group D</td>
<td>RELAz</td>
<td>Survived</td>
</tr>
</tbody>
</table>

\(^\text{a}\)Treatment combinations: R = rifampin, E = ethambutol, C = clarithromycin, Az = Azithromycin, M = moxifloxacin, L = levofloxacin, A = amikacin, S = streptomycin, IFN-γ = interferon gamma, NA = not available

\(^\text{b}\)Patients 1-9, 10-12, and 13 were adapted from reference 6, 17 and unpublished data, respectively
Table 2. Summary of reported adjunctive treatments for autoantibody to IFN-γ.

<table>
<thead>
<tr>
<th>Modality/No. of patient</th>
<th>Indications and dose administration</th>
<th>Efficacy and comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti CD20 (rituximab)/4 patients*</td>
<td>- Relapsed or refractory cases over 1 year of treatment, - Varying dose administration between 8 to 12 doses within the first year to maintain disease remission, - Subsequent doses were given for relapsed infection</td>
<td>- Clearance of bacteremia, improved bone lesions, weight gain, and 58-80% decrease of autoantibody to IFN-γ level from baseline</td>
<td>25</td>
</tr>
<tr>
<td>Intravenous Immunoglobulin (IVg)/1 patient</td>
<td>- Antimycobacterial treatment not responsive over 3 months, - IVg 0.4 g/kg/day for 5 days plus surgical drainage</td>
<td>- Improvement in symptoms, level of CRP and WBC count, and size of lesion</td>
<td>11</td>
</tr>
<tr>
<td>Plasmapheresis plus cyclophosphamide/1 patients</td>
<td>- Recurrent multifocal MAC infection, - Plasmapheresis, cyclophosphamide and quadruple antimycobacterial chemotherapy</td>
<td>- Decrease of autoantibody to IFN-γ, - Clinical remission after 3 years of follow-up</td>
<td>15</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein, IFN-γ = interferon gamma, WBC = white blood cell

*Rituximab doses 375 mg/m² weekly for at least 4 doses and then at a wider intervals

pheresis with pulse cyclophosphamide, and IFN-γ were also reported as the additional treatment, but the treatment outcomes were varied among cases. To our knowledge, there have no curative treatments for pathogenic IFN-γ autoantibody. The disease remained unfavorable outcomes. Most of patients had persistent or relapsed infection. Further studies for an optimal treatment are needed to improve the clinical outcome.

**CONCLUSION**

Autoantibody to IFN-γ should be considered in a HIV-negative adult who severely infected with *M. avium* infection. The clinical features usually manifests as disseminated infection and chronic recurrent infection. A long-term combination of anti-mycobacterial agents is a mainstay of treatment. Immunosuppressive and/or immunomodulatory agents as adjunctive therapy for prevention of relapsed disease should be further studied to optimize the outcome.

**References**

1. Rossi M, Flepp M, Telenti A, et al. Disseminated *M. avium* complex infection in the Swiss HIV Cohort Study: declining incidence, improved prognosis and


