R-CHOP chemotherapy for disseminated *Mycobacterium avium* complex disease due to anti-interferon-gamma autoantibodies: A case report

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Abstract

A 77-year-old Japanese man with disseminated *Mycobacterium avium* complex (MAC) disease due to anti-interferon-gamma autoantibodies received R-CHOP chemotherapy because of non-Hodgkin lymphoma complication. The hepatobiliary nodules due to MAC resolved with R-CHOP along with multidrug anti-mycobacterial treatment. R-CHOP would serve as an alternative adjunctive therapy for patients with anti-interferon-gamma autoantibodies.

Keywords: anti-interferon-gamma autoantibody; disseminated *Mycobacterium avium* complex diseases; cyclophosphamide; rituximab; R-CHOP.
Introduction

Neutralizing anti-interferon-gamma (IFN-γ) autoantibodies are reported as a predisposing factor for treatment-refractory disseminated nontuberculous mycobacterial infections [1]. Reports of this adult-onset immunosuppressive syndrome are relatively frequent in East Asia, including Japan, Taiwan, and Thailand [2-4]. Various challenges with rituximab, cyclophosphamide, and daratumumab have been encountered on this acquired immunodeficiency disease [5-8]; however, its specific treatment is not yet been codified.

We have previously reported that a Japanese man with anti-IFN-γ autoantibodies developed obstructive jaundice due to hepatobiliary Mycobacterium avium complex (MAC) infection [9]. He later developed non-Hodgkin lymphoma, and thus, the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) treatment was initiated. Here, we report the clinical course and the transition of anti-IFN-γ antibodies.

Case description

As we previously described [9], a 74-year-old man at that time without human immunodeficiency virus (HIV) infection presented with recurrent multiple lymphadenopathy with MAC in the repeated culture of biopsy samples. He was treated with anti-mycobacterial agents, including clarithromycin of 800 mg, rifampicin 600 mg, ethambutol 500 mg, and sitafloxacin 200 mg per day for 4 years. However, obstructive jaundice and cholangitis subsequently occurred due to biliary stricture caused by intrahepatic nodules. The culture of both his liver biopsy nodule specimen and bile showed MAC. He was confirmed to have neutralizing anti-IFN-γ autoantibodies thereafter. Choledochoduodenal
stent was placed, which improved his condition without changing the anti-mycobacterial treatment regimen. In Japan, rituximab has not been approved to be used for IFN-γ autoantibodies; thus, rituximab was not administered.

After 2 years, his cervical lymph nodes had swollen again. His vital signs were stable without fever, fatigue, or weight loss. Lymph node biopsy resulted in the diagnosis of diffuse large B-cell lymphoma and negative for Epstein–Barr virus (EBV)-encoded small RNAs (EBER). Positron emission tomography–computed tomography (PET-CT) revealed strong uptake (SUV\text{max}) at the left supraclavicular lymph nodes (29.0), liver (41.1), spleen (31.0), intestine (13.6), and right ischial bone (8.9) in addition to the weak uptake in the liver (5.1) that has previously existed, which was diagnosed as intrahepatic nodules caused by MAC. He was diagnosed with stage IVA diffuse large B-cell lymphoma.

He then received six cycles of R-CHOP chemotherapy once every 3 weeks with four anti-mycobacterial medications. We sequentially stored his serum and measured anti-IFN-γ autoantibodies during and after chemotherapy using an enzyme-linked immunosorbent assay as previously described [10] (Fig. 1A). Anti-IFN-γ antibodies gradually decreased during the R-CHOP chemotherapy; however, it increased again at the end of R-CHOP.

The physician was concerned that R-CHOP chemotherapy would cause intestinal perforation amid his intestinal invasion of lymphoma and exacerbations of the disseminated MAC diseases. Thus, CHOP doses, except for rituximab for 375 mg/m\textsuperscript{2}, were reduced to 50%: cyclophosphamide, 375 mg/m\textsuperscript{2}; doxorubicin, 25 mg/m\textsuperscript{2}; vincristine, 0.7 mg/m\textsuperscript{2}; and prednisolone, 50 mg for 5 days. Co-trimoxazole was also administered for pneumocystis pneumonia prophylaxis during chemotherapy and pegfilgrastim from the fourth cycle for
neutropenia. No other adverse events had been observed during chemotherapy. After the R-CHOP treatment was completed, the anti-mycobacterial treatment was continued.

After six cycles of chemotherapy, he was diagnosed as complete remission due to the absence of uptake on PET–CT. The previously noted intrahepatic lesions, diagnosed as MAC nodules by liver biopsy, were also invisible on PET–CT (Fig. 1B). Thus, the R-CHOP treatment was effective against both lymphoma and disseminated MAC infections, including intrahepatic lesions. He had been in a steady state for the next 3 years.

Discussion

This is the first to report on R-CHOP chemotherapy with anti-mycobacterial treatment that, along with lymphoma, effectively managed disseminated MAC diseases with neutralizing anti-IFN-γ antibodies. Immunosuppression such as HIV infection, solid organ or bone marrow transplantation, various immunosuppressive agents, or primary immune disorders was correlated with the development of lymphoproliferative disorders [11]. In previous case reports, patients with complete IFN-γ receptor 1/2 deficiency developed B-cell lymphoma associated with EBV [12], Kaposi sarcoma associated with human herpes virus-8 [13], and esophageal carcinoma associated with human papilloma virus [14], were previously reported. According to a previous observational study, 4 out of 45 patients with anti-IFN-γ autoantibodies developed malignancies originated from the T-cell/Macrophage lineage [2]; however, the relationship between neutralizing anti-IFN-γ antibodies and development of malignancies was not well known. The fact that EBER was negative in the excised lymph node specimens in this case suggested the possibility of EBV-unrelated B-cell
lymphoma. R-CHOP chemotherapy may be a promising treatment of choice for anti-IFN-γ autoantibody-positive individuals with lymphoma complications.

R-CHOP, which is the standard chemotherapy against B-cell lymphoma, induces immediate decreases in serum immunoglobulin G (IgG) after R-CHOP treatment and subsequent restoration over 2 years [15]. In the present case, IFN-γ autoantibodies and IgG decreased simultaneously. Immunity mediated by IFN-γ and interleukin 12 plays a critical role in the biological defense against nontuberculous mycobacterial infection [2-4]. We speculated that when the defensive capacity against MAC was impaired because of the presence of IFN-γ autoantibodies, R-CHOP administration temporarily suppressed such autoantibodies, leading to the restoration of the immune function of IFN-γ. Therefore, the anti-mycobacterial treatment was more effective, resulting in the healing of the lesions caused by MAC.

Rituximab treatment had firstly been reported as an adjunctive therapy to anti-mycobacterial drugs for neutralizing anti-IFN-γ autoantibodies [5]. Intravenous cyclophosphamide was also administered as an adjunctive therapy especially in resource-limited settings [7]. The use of daratumumab, an anti-CD38 monoclonal antibody targeting plasma cells approved for the treatment of multiple myeloma, was also recently reported, and its effect in modulating humoral immunity might benefit patients with some immunodeficiency diseases [8]; however, no reports on long-term antibody trends nor its relationship with relapsed disseminated nontuberculous mycobacterial diseases have been reported. In this case, the previously observed intrahepatic lesions, diagnosed as MAC nodules by liver biopsy, were resolved on PET–CT after R-CHOP chemotherapy; however, anti-IFN-γ autoantibodies increased again. Whether the re-elevation of anti-IFN-γ
autoantibodies was common with other adjunctive treatments remains unclear; however, R-CHOP chemotherapy was assumed to be effective as the lesions were resolved.

This case should be interpreted in light of several limitations. First, this study is a case report and its external validity still needs to be evaluated. R-CHOP chemotherapy including both rituximab and intravenous cyclophosphamide can be expected as an adjunctive therapy for anti-IFN-γ autoantibodies; however, the timing and dosage might need to be adjusted due to the re-elevation of antibodies at the end of the study. The necessity for doxorubicin and vincristine should also be further elucidated. Furthermore, considering that R-CHOP is a chemotherapy, adverse effects, such as myelosuppression, which was experienced by our patient, should be carefully monitored. Anyhow, we speculated that the combination of these two might also increase the likelihood of disease improvement especially for patients not treated by a single agent or patients with lymphoma complications.

In conclusion, the R-CHOP chemotherapy can be potentially used as a novel adjunctive therapy to anti-mycobacterial therapy for patients with disseminated nontuberculous mycobacterial diseases due to anti-IFN-γ autoantibodies.
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Author contributions: Shunsuke Uno designed the study, analyzed, and drafted the manuscript; Eisuke Uehara was the physician in charge of the patient treatment; Toshiki Kimura, and Takuro Sakagami measured the anti-interferon-gamma autoantibodies, confirmed the analyses, and participated in editing the manuscript; Ho Namkoong, Sho Uchida, and Yoshifumi Uwamino revised the article for intellectual content; and Naoki Hasegawa, who was also the physician in charge of the patient treatment, revised the article for intellectual content. All authors read and critically revised the first as well as the subsequent and final drafts of this manuscript.
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**Figure legend**

**Fig. 1.** A: The transition of total immunoglobulin G (IgG) and anti-IFN-γ autoantibodies. R-CHOP administration is indicated in arrows. The month of diffuse large B-cell lymphoma diagnosis was set to 0. B: PET–CT images before and after the R-CHOP treatment (a) when diagnosed with hepatobiliary MAC disease, 2 years before the diagnosis with lymphoma and (b) when diagnosed with diffuse large B-cell lymphoma (c) 1 month after the last R-CHOP chemotherapy.
