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BRIEF REPORT

R-CHOP Chemotherapy for Disseminated *Mycobacterium avium* Complex Disease due to Anti-Interferon-Gamma Autoantibodies: A Case Report

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

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

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 in Japan, Taiwan, and Thailand [2–4]. Various challenges with rituximab, cyclophosphamide, and daratumumab have been encountered in this acquired immunodeficiency disease [5–8]; however, its specific treatment is not yet been codified.

We 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 treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) 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 HIV infection presented with recurrent multiple lymphadenopathy with MAC on repeated culture of biopsy samples. He was treated with antimycobacterial agents, including clarithromycin 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. A choledochoduodenal stent was placed, which improved his condition without changing the antimycobacterial treatment regimen. In Japan, rituximab has not been approved for use in patients with 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 diagnosis of diffuse large B-cell lymphoma and was negative for Epstein-Barr virus (EBV)–encoded small RNAs (EBER). Positron emission tomography–computed tomography (PET-CT) revealed strong uptake (SUV_{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 had 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 6 cycles of R-CHOP chemotherapy once every 3 weeks with 4 antimycobacterial 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 (Figure 1A) [10]. Anti-IFN-γ antibodies gradually decreased during the R-CHOP chemotherapy; however, they increased again after the end of R-CHOP.

The physician was concerned that R-CHOP chemotherapy would cause intestinal perforation amid his intestinal invasion of lymphoma and exacerbate the disseminated MAC disease. Thus, the CHOP doses, except for rituximab for 375 mg/m^2, were reduced to 50%: cyclophosphamide 375 mg/m^2, doxorubicin

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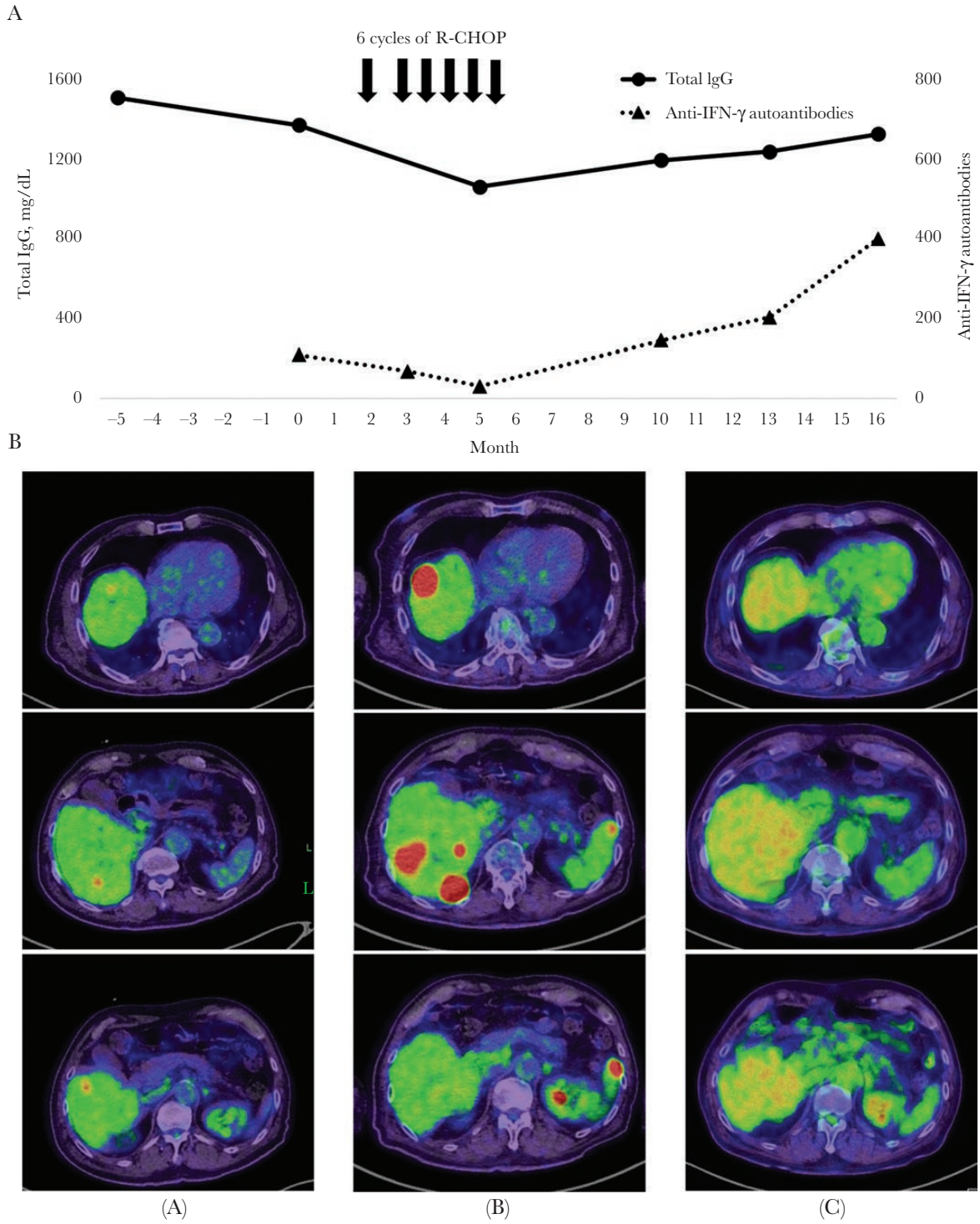

Figure 1. A, The transition of total IgG and anti-IFN-γ autoantibodies. R-CHOP administration is indicated in arrows. The month of diffuse large B-cell lymphoma diagnosis was set to 0. B, PET-CT images before and after the R-CHOP treatment: (a) when diagnosed with hepatobiliary MAC disease 2 years before the diagnosis with lymphoma and (b) when diagnosed with diffuse large B-cell lymphoma (c) 1 month after the last R-CHOP chemotherapy. Abbreviations: IFN, interferon; IgG, immunoglobulin G; MAC, *Mycobacterium avium* complex; PET-CT, positron emission tomography–computed tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

25 mg/m^2, vincristine 0.7 mg/m^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 were observed during chemotherapy. After the R-CHOP treatment was completed, antimycobacterial treatment was continued.

After 6 cycles of chemotherapy, he was diagnosed as being in 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 (Figure 1B). Thus, the R-CHOP treatment was effective against both lymphoma and disseminated MAC infections, including intrahepatic lesions. He was in a steady state for the next 3 years.

DISCUSSION

This is the first report on R-CHOP chemotherapy with antimycobacterial 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 papillomavirus [14]. According to a previous observational study, 4 out of 45 patients with anti-IFN-γ autoantibodies developed malignancies that originated from the T-cell/macrophage lineage [2]; however, the relationship between neutralizing anti-IFN-γ antibodies and development of malignancies is 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 antimycobacterial treatment was more effective, resulting in the healing of the lesions caused by MAC.

Rituximab treatment was first reported as an adjunctive therapy to antimycobacterial drugs for neutralizing anti-IFN-γ autoantibodies [5]. Intravenous cyclophosphamide has also been 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 or relationship between relapsed disseminated nontuberculous mycobacterial diseases and long-term antibody trends 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 is common with other adjunctive treatments remains unclear; however, R-CHOP chemotherapy was assumed to be effective as the lesions 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. We speculated that the combination of these 2 might also increase the likelihood of disease improvement especially for patients not treated by a single agent or patients with lymphoma complications.

In conclusion, R-CHOP chemotherapy can be potentially used as a novel adjunctive therapy to antimycobacterial therapy for patients with disseminated nontuberculous mycobacterial diseases due to anti-IFN-γ autoantibodies.

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