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ORIGINAL ARTICLE

Serum Anti-interferon-γ Autoantibody Titer as a Potential Biomarker of Disseminated Non-tuberculous Mycobacterial Infection

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Abstract

Purpose In the past decade, the relationship between naturally occurring interferon-γ-neutralizing autoantibodies (IFNγ-Ab) and disseminated non-tuberculous mycobacteria (NTM) infection has been established. Furthermore, immune suppressive therapy aimed at the suppression of antibody production has shown efficacy as a supportive treatment. However, the nature of antibody behavior and antibody titer during the course of this disease, as well as the pathophysiological significance of IFNγ-Ab, has not yet been fully elucidated.

Methods Thirteen Japanese subjects suffering from disseminated NTM (dNTM) infection with IFNγ-Ab were evaluated. The fluctuation of IFNγ-Ab titer and the neutralizing capacity against IFN-γ during the course of the disease were retrospectively analyzed. IFNγ-Ab titers in the sera were quantified using an enzyme-linked immunosorbent assay; neutralizing capacity was evaluated via flow cytometry.

Results Serum antibody titers were not constant during the treatment period and varied over the course of the disease. The antibody titer decreased when the disease was improved by anti-mycobacterial treatment ($p < 0.01$) and increased as the disease progressed ($p < 0.05$). Even after the antibody titer decreased, the neutralizing capacity against IFN-γ was maintained by individual sera.

Conclusions Despite the improvement in the pathological condition via treatment, the patients' sera maintained neutralizing capacity against IFN-γ. Antibody titer fluctuated over the course of the disease and exhibited potential as a biomarker for judgment of the disease state.

Keywords Disseminated NTM · neutralizing capacity · biomarker · serum interferon-γ autoantibody titer

Introduction

Interferon-γ-neutralizing autoantibodies (IFNγ-Ab) have been detected in more than 80% of disseminated non-tuberculous mycobacterial (NTM) infection cases without an apparent pathological background leading to immunodeficiency [1–3]. The diagnosis of this condition is often difficult as these cases do not show characteristic clinical symptoms [3, 4]. In addition, treatment requires the use of a combination antibiotic chemotherapy over a long period. IFNγ-Ab was not detected in cases with pulmonary NTM and instead was detected in disseminated NTM (dNTM) [1, 3, 5], disseminated or recurrent salmonellosis [6–8], and toxoplasmosis [8]. This suggested that there might be an acquired disease-specific autoantibody associated with these diseases. While there is less than robust scientific evidence available, it has been broadly accepted that the autoantibody is one of the susceptibility factors for these diseases. In a practical situation, it has been reported that suppressing antibody production by treatment with rituximab [9–14] or cyclophosphamide [15] was performed in some intractable cases, and these medications produced favorable effects.

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Furthermore, unresolved questions about the nature of IFNγ-Ab remain, including why the antibody is produced, how the amount of production is controlled, and how the antibodies behave in vivo. To date, all that has been reported for the behavior of IFNγ-Ab is that there is no correlation between the initial antibody titer and the severity of dNTM disease [16, 17] and that the autoantibody titer is decreased over time among patients with drug-free remission [17]. We also have very limited information about the appropriate duration of treatment for NTM infection. Although the majority of cases could be improved with long-term anti-mycobacterial chemotherapy, there were no clinical indicators subsequent to treatment interruption. It is important to discover the indicators because all of the cases who terminated their anti-mycobacterial treatment after disease remission experienced a relapse of their NTM infection in our previous report [3].

Therefore, understanding the behavior of IFNγ-Ab, the nature of this autoantibody, and the development of biomarkers is important for the determination of the optimal treatment duration in the clinical setting. In order to elucidate these clinical questions, we hypothesized that the behavior of the IFNγ-Ab titer could be a biomarker which reflected the clinical condition of the dNTM infection and analyzed IFNγ-Ab titers in the sera over time among the dNTM cases carrying IFNγ-Ab.

Methods

Subjects and Evaluation of Clinical Course

This study was performed with the approval of the Ethics Committee at the School of Medicine, Niigata University (Approval number; 1413), and complied with the Declaration of Helsinki. All subjects provided informed consent.

From May 2012 to May 2018, we recruited subjects suffering from dNTM disease with IFNγ-Ab and accumulated their clinical data. Disseminated NTM disease was defined when samples from more than one lesion or when clinically sterile samples such as blood and bone marrow yielded positive cultures for NTM. The medical records of subjects with dNTM were reviewed and extracted into a standardized format by their attending physicians. We do not have authorized or established guidelines to determine dNTM disease activity. Therefore, the course of the disease in an individual patient during treatment was judged by careful and comprehensive observation based on signs of active infection and symptoms, as well as physical and laboratory examinations. Then they were recorded using the terms improved, stable, or deteriorated.

Measurement of IFNγ-Ab Titer and the Neutralizing Capacity against IFN-γ

The evaluation of relative IFNγ-Ab concentration in the sera and the neutralizing capacity against IFN-γ were conducted by following methods that were described previously [3, 18]. Briefly, in each experiment, sera from healthy volunteers without any relevant disease served as controls. Serum IFNγ-Ab concentration was quantified by using an enzyme-linked immune sorbent assay (ELISA), which was performed using commercially available mouse anti-human interferon-γ monoclonal antibody (Abcam plc. UK. #ab10076) as a standard for quantitation. We used the term Elisa Unit (E.U.) as a unit. One E.U. was identical to 1.0 ng/mL of the standard antibody. Furthermore, the relative titer of IFNγ-Ab was described as the ratio of antibody titer from the pooled sera of the healthy controls. Plate-to-plate variation has been a concern for our quantification method (Figure S1a) because a suitable reference antibody has not yet been established. In order to avoid these variations, we used the results of simultaneous measurements on the same plate, which compared the results at different time points for each case.

The neutralizing capacity against IFN-γ was evaluated using a flow cytometry–based analysis previously described [3]. Briefly, Jurkat cells inoculated with 90 μL of sera that was diluted 100-fold with phosphate-buffered saline were stimulated with 10 ng/mL recombinant human IFN-γ (Wako Co. Ltd., Gunma, Japan). Following incubation, cells were fixed and permeabilized with 95% methanol. The permeabilized cells were stained with anti-mouse phospho-signal transduction and the activator for the transcription 1 (STAT1) antibody (Alexa Fluor 647 Mouse Anti-STAT1 (pY701), BD Biosciences). Positive cells with phosphorylated STAT1 were identified using FACS Calibur (BD Bioscience) and analyzed using CellQuest Pro software (BD Bioscience). The STAT1 phosphorylation index (STAT1-PI) was calculated following a method previously reported [3]. Results were described as a relative value to the healthy subjects, because of variation between experiments (Figure S1b).

Statistical Analysis

Data were analyzed using the SigmaPlot (version 12.3; Systat Software Inc., San Jose, CA) software. The comparison of changes in the antibody concentration and STAT1-PI of an individual subject was performed using the one-tailed paired *t* test or Wilcoxon signed-rank test if the normality test was passed or not, respectively. A p value of less than 0.05 was considered to be statistically significant.

Results

Overview of Changes in the IFN-γ Autoantibody Titers in the Sera

We recruited 77 Japanese adult subjects who were suffering from dNTM. IFNγ-Ab was detected in 47 of 77 subjects. Thirty-four of the 47 subjects were excluded from further analysis and were measured for IFNγ-Ab titer just once. The rest of the 13 subjects were selected for further evaluation and tested for IFNγ-Ab titer multiple times. The diagram for inclusion in the analysis is depicted in Fig. 1. Four of the subjects were treated with corticosteroids, and 2 had received rituximab treatment. Two of the subjects had herpes zoster, and one had toxoplasmosis in their medical history. Twelve of the 13 cases were included in our previous report [3]. Their attending physicians had provided data regarding each patients' clinical course over time. Background for the 13 subjects is shown in Table 1. The median age of onset was 66.0 (interquartile range (IQR), 60.5–69.0) years old. Nine subjects were male, and four subjects were female. Isolated mycobacterial species included *Mycobacterium avium* complex ($n = 10$), *Mycobacterium abscessus* complex ($n = 2$), *Mycobacterium gordonae* ($n = 2$), and *Mycobacterium mantenii* ($n = 1$). Two species were isolated in two subjects simultaneously. All of the patients were administered multiple anti-mycobacterial agents, including macrolides. Among the 13 subjects, IFNγ-Ab was measured 44 times in total. We could evaluate changes in the IFNγ-Ab titer at 31 intervals between the measurement points. The whole measurement data was described in Table S1. The median baseline antibody titer for the subjects was 57.1 times higher than that in the healthy controls (IQR, 11.2–124.0 times). Percentage changes in the antibody titer within the individual sera from the baseline measurement were assessed over time (Fig. 2). Subjects in which the antibody titer decreased from the initial measurement over time were more prevalent than those where the antibody titer had increased. However, some cases showed a decline in antibody concentration after increasing, while other cases increased after declining initially. IFNγ-Ab titers in the sera fluctuated during the clinical course.

Association Between Clinical Course and IFNγ-Ab Titer in Sera

We analyzed the relationship between the clinical course and the behavior of antibody titers. Changes in the IFNγ-Ab titer from the previous measurement point were described in Figure S2. The antibody titers tended to increase when the disease condition had deteriorated, and they decreased when the disease condition had improved. When the subjects were administrated corticosteroids or immunosuppressants, the

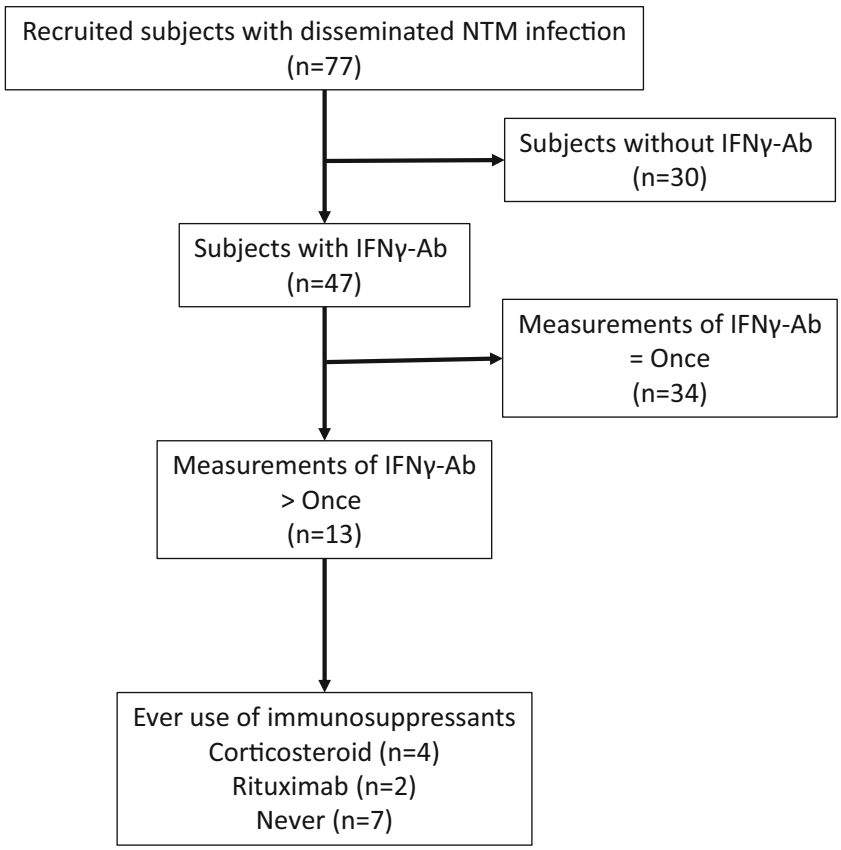

Fig. 1 Flow diagram for study inclusion

Table 1 Clinical characteristics of the analyzed subjects

Features	($n = 13$) Value
Demographics	
Age, years, median (IQR)	66 (60.5–69)
Sex, female/male, No.	4/9
BMI, kg/m2, median (IQR)	21.1 (17.8–23.0)
History of immunosuppressant use, No. (%)	6 (46.1)
Laboratory data, median (IQR)	
Total protein, g/dL	7.1 (5.8–7.8)
Albumin, g/dL	2.9 (2.5–3.2)
CRP, mg/dL	5.6 (2.4–15.2)
WBC count, /μL	12,255 (8317–17,950)
Neutrophils, %	78.0 (61.0–87.0)
Lymphocyte, %	13.0 (8.5–23.5)
Site of involvement, No. (%)	
Lung	8 (61.5)
Bone marrow, blood	8 (61.5)
Lymph nodes	7 (53.8)
Bone, joint	6 (46.1)
Muscle	3 (23.0)
Spleen, liver	2 (15.4)
Urinary organ	2 (15.4)
Skin	1 (7.6)

BMI, body mass index; *CRP*, C-reactive protein; *IQR*, interquartile range

antibody titer decreased significantly regardless of the disease course (1274 ± 2682 E.U. to 184 ± 206 E.U., $p < 0.05$) (Table S1). The use of these agents was considered to have an effect on IFNγ-Ab titers. Therefore, measurement points when the individual had received these agents within 3 months were excluded from further analysis. Ten intervals of data from 6 cases were excluded, and analysis was conducted using 21 intervals from the remaining 12 subjects. We classified the change in disease condition between measurements into the following three groups improved, stable, and deteriorated (number of data points from the two measurements was 10, 6, and 5, respectively), which were classified according to the reports from their attending physicians. While IFNγ-Ab titers were significantly decreased (983 ± 1112 E.U. to 478 ± 739 E.U., $p < 0.01$) in the group with the improved condition (Fig. 3a), the antibody titer did not change in the group where the disease state was stable (1648 ± 893 E.U. to 1319 ± 857 E.U., N.S.) (Fig. 3b). However, titer was significantly elevated in the group with deterioration in their disease condition (430 ± 726 E.U. to 959 ± 1060 E.U., $p < 0.05$) (Fig. 3c). These results suggested that IFNγ-Ab titers were correlated with the course of dNTM disease.

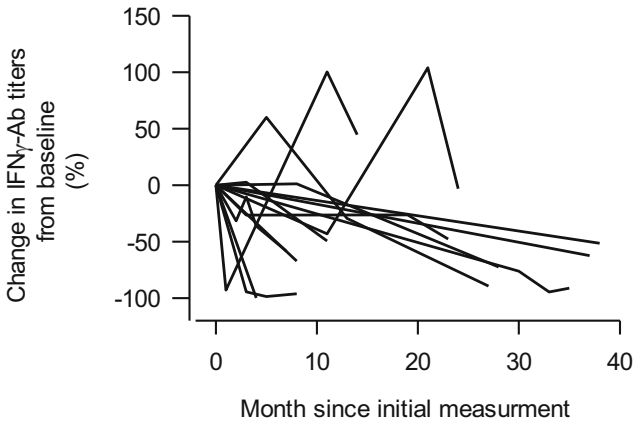

Fig. 2 Overview of changes in the IFNγ-Ab titers for individuals. Percent changes in the autoantibody titers in sera from the baseline measurement in 13 individuals over time were described

IFN-γ Autoantibodies Titer and Neutralizing Capacity Following Anti-mycobacterial Treatment

Changes in the individual neutralizing capacity at two time points when the antibody titer had decreased were assessed. The antibody titer ratio compared with the healthy controls decreased significantly between the initial and later measured points (250 ± 398 times to 50 ± 90 times, $p < 0.01$). Three cases showed a decrease in IFNγ-Ab titers to 75% or less of the healthy controls (Fig. 4). Similar to the decreases in the IFNγ-Ab concentrations, the relative value of STAT1-PI compared with that of the post-treatment controls was also significantly increased ($2.3 \pm 4.7\%$ to $16.1 \pm 33.8\%$, $p < 0.01$) and was interpreted as "improved." However, after improvement of the neutralizing capacity in the sera, the relative value of STAT1-PI was just 16.1% to the normal subjects. Additionally, improvement in the neutralizing capacity up to the normal level was observed in only one case and was maintained in the other cases. Thus, they were considered to possess significant biological neutralizing capacity against IFN-γ, after the antibody concentrations had decreased.

Discussion

In this study, we observed changes in antibody titer overtime for 13 dNTM cases with IFNγ-Ab. As a result, it was revealed that IFNγ-Ab titers were not constant and fluctuated throughout treatment. Serum titer for IFNγ-Ab changed in relation to the course of the disease condition. IFNγ-Ab titer decreased significantly when the disease condition improved and increased significantly when it deteriorated. Thus, our longitudinal assessment during medical treatment has revealed that the behavior of the serum IFNγ-Ab titer could be a biomarker reflecting the disease condition. Serial measurement and monitoring of antibody titer in an individual could make it possible to determine the therapeutic effect, expected clinical outcome, or the possibility of relapse into NTM disease.

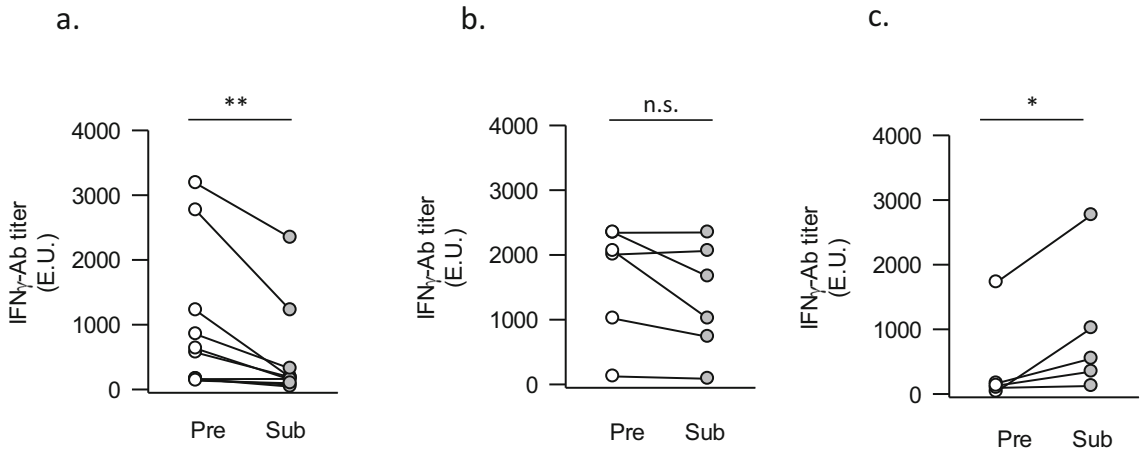

Fig. 3 Association between clinical response and IFNγ-Ab titer in sera. IFNγ-Ab titers in the sera are quantified in an identical plate by ELISA. **a** When dNTM disease was improved, the titers were decreased significantly ($p < 0.01$). **b** When dNTM disease was stable, the titers were similar. **c** When dNTM disease had deteriorated, the titers increased significantly ($p < 0.05$). White and gray circles indicate the previous and subsequent values for each measurement interval, respectively. Pre, previous measurement; Sub, subsequent measurement. Single asterisk indicates $p < 0.05$, and double asterisk indicates $p < 0.01$

The association between the behavior of the IFNγ-Ab titer and the disease course of patients with dNTM provided an important suggestion to the nature of IFNγ-Ab. The reason for the increase or decrease of IFNγ-Ab concentrations in the sera corresponded to the disease course and might be the result that corresponded to the fluctuation amount of the IFN-γ in the individuals. We proposed hypothetical mechanisms which could drive IFNγ-Ab production in Fig. 5. We did not elucidate the fundamental mechanisms used to escape from immunological tolerance to IFN-γ protein, which is a self-antigen, although molecular mimicry to the noc2 protein of *Aspergillus* species has been proposed as a promising hypothesis [19]. Production of autoantibodies, induced by unknown mechanisms, occurs in the presence of memory B cells that recognize the epitope of the IFN-γ protein. When a certain number of autoantibodies are produced, individuals will acquire susceptibility to NTM disease. Under this situation, NTM could infect individuals easily, and then the host defense mechanisms against intracellular microbes promoted IFN-γ production. Memory B cells might be stimulated and differentiated into plasma cells [20] depending on the excess amount of antigen available under the coordinate with antigen-specific helper T cells [21, 22]. As a result, production of autoantibodies could be accelerated, and the IFNγ-Ab titer increased. When the condition of NTM disease is improved by anti-mycobacterial chemotherapy, the amount of IFN-γ production naturally decreased, which led to a reduction in IFNγ-Ab production. Other possible explanation as to why the IFNγ-Ab titer reduced is that the internal activation of IFN-γ that formed an excess amount of immune-complex decreases the amount of free IFNγ-Ab. Also, as described in the limitation, our ELISA system might have a potential low precision. Therefore, it is undeniable that we observed that the variation in antibody titer depending on the disease course is a variety of non-specific reactions in the ELISA method associated with hyper-γ-globulinemia. However, the possibility might be low because there was no correlation between the antibody titer and the serum albumin/globulin ratio (data not shown).

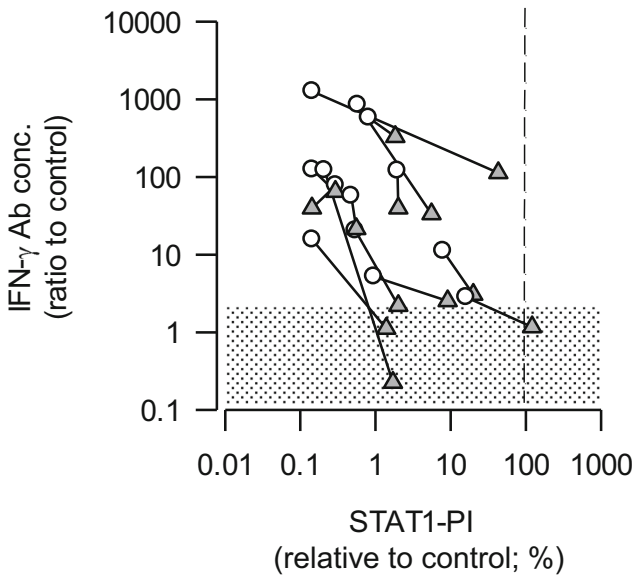

Fig. 4 Neutralizing capacity against IFN-γ corresponding to serum IFNγ-Ab titers. The changes in neutralization capacity when the antibody titer decreased are described. The neutralizing capacity against IFN-γ was also improved ($p < 0.01$) corresponding to the antibody titer decreased; however, almost all cases did not improve to the level of the healthy controls. White circles indicate the initial point gray triangles indicate later point of measurement, respectively. The shaded area represents the 75% percentile antibody concentration range of the healthy controls (median, 0.584; IQR, 0.379–1.262)

Even after the antibody titer decreased, the biological neutralization capacity of IFN-γ was maintained in our investigation. There could be a potential difference in the sensitivity to

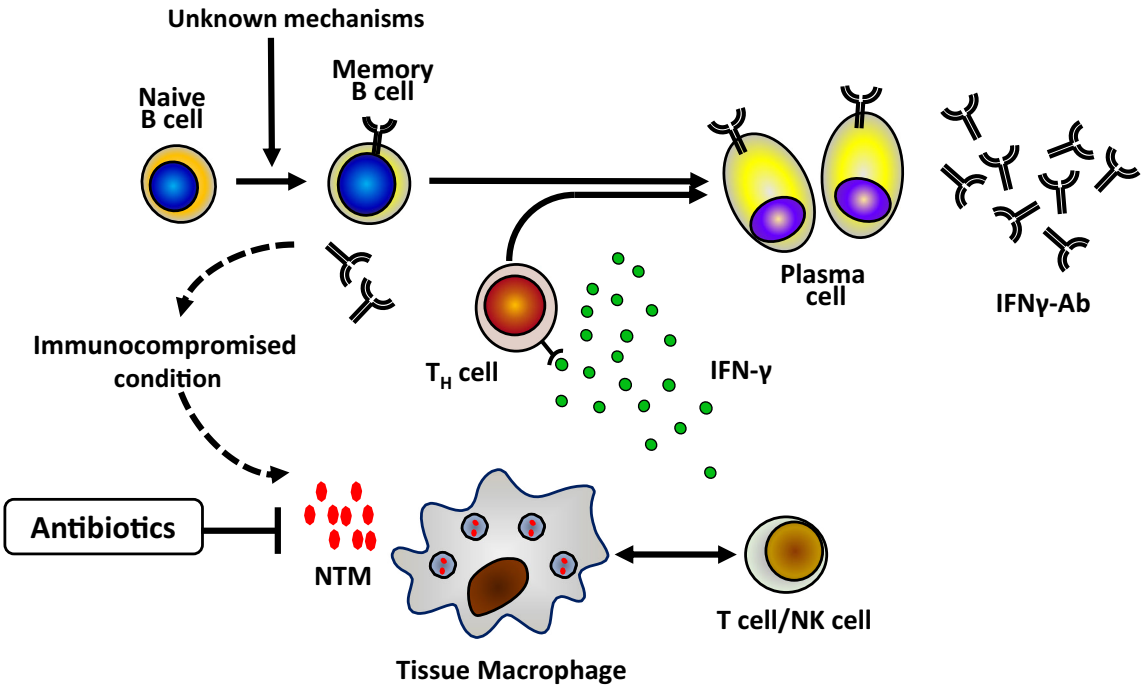

Fig. 5 Proposed mechanisms driving IFNγ-Ab production

detect IFNγ-Ab between our ELISA and flow-based analysis. In particular, since our ELISA is a relative evaluation, it is considered that sensitivity within a low concentration range might be low. Conversely, when the qualitative sensitivity of our flow cytometry–based method was high, there could be a possibility that results like our observation were obtained. In any case, our results indicated that susceptibility to NTM infection might be persistent for a while in the host. In fact, it has been reported that all of the patients developed recurrent NTM disease when antibacterial therapy was terminated due to remission [3]. Based on these results, we suggested that the remaining neutralizing capacity was above the critical threshold for disease onset. Furthermore, while the optimal duration of the anti-mycobacterial treatment has not yet been established, our data provided one suggestion that it is not desirable to interrupt treatment after remission, and continuous prophylaxis might be necessary.

The present study had some limitations. First, the number of subjects was small, because disseminated NTM with IFNγ-Ab cases are rare. Furthermore, patients with antibody titers that could be quantified consecutively were extremely rare. Second, we could not show clear and objective criteria for determining the individuals' disease course. Since the decision was made by the subjectivity of the attending physician, it cannot be denied that it was not consistent with the pathological improvement of the dNTM infection. Third, the measurement method we used was an ELISA, and we did not have a reference antibody to determine the absolute value of the antibody titers. As a result, plate-to-plate variation has been a concern. To avoid this plate-to-plate variation, we used the results of simultaneous measurements on the same plate, to compare the results from different time points for each case. Fourth, this was a retrospective observational study, and selection bias existed because this study involved the convenience of samples. Therefore, we should develop the established measurement method for IFNγ-Ab, and a longitudinal prospective nationwide study should be conducted to clarify the relationship between the behavior of the antibody titer and the course of the disease.

Conclusions

In summary, we found that IFNγ-Ab titers were not constant and fluctuated to reflect the course of disseminated NTM disease. Further, following our proposed mechanism to regulate autoantibody production, IFNγ-Ab titers might have fluctuated above the threshold for susceptibility to NTM disease. Finally, we concluded that the behavior of IFNγ-Ab was a clinically useful biomarker for the judgment of the course of dNTM disease during treatment.

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Authorship Contributions All authors contributed to the conception and design of the study. KY, AA, and KS coordinated the investigation of subjects' sample analysis. KY and TS performed data analysis and interpretation. TS drafted the manuscript. KY, YT, TK, TH, TK, and TS reviewed the manuscript critically. All authors read and approved the final manuscript.

Conflict of Interest The authors declare that they have no conflict of interest.

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Compliance with Ethical Standards This study was performed with the approval of the Ethics Committee at the School of Medicine, Niigata University (Approval number; 1413), and complied with the Declaration of Helsinki. All subjects provided informed consent.

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