Abstract of Master's Dissertation

Course	Tropical medicine	Name	Yumiko Hayashi

Thesis Title	Cytokine responses of Filipino active TB patients with diabetes mellitus, hyperglycemia or malnutrition to TB antigens

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Objective :

Tuberculosis (TB) is one of the three main causes of death due to infectious disease beside HIV and malaria, in low- and middle-income countries. However, there is no effective prevention against TB yet. These days, the prevalence of non-communicable diseases, especially diabetes (DM), is increasing and affects on TB pathology. TB patients in the Philippines, the 4th high endemic country globally, suffer from the comorbidity with DM or malnutrition. Although this situation is known to be associated with worse treatment outcomes, the reasons are not well known. Defects in immune responses are suspected so far. Therefore, two objectives set for 1.) gaining insight how cytokine responses to TB antigens are altered under hyperglycemia induced by diabetes (mild DM: $6.5\% \leqq$ HbA1c<8.0%, severe DM: $8.0\% \leqq$ HbA1c) and 2.) gaining insight how cytokine responses to TB antigens are altered under malnutrition (BMI: body mass index<17kg/m^2 vs healthy weight patients).

Method :

Study design is case-control study embedded in Starting anti-TB treatment study (St-ATT study). 135 blood samples of active TB patients were collected from St-ATT study in the Philippines between November 2018 and December 2019. Blood samples were stimulated by TB specific antigens to assess cytokine responses. In this study, cytokine responses (IFN-γ, IL-2, IL-10, and IL-17A) were quantified with multiple beads assays. Laboratory data was combined with clinical information by St-ATT study and analyzed with STATA. The data was treated as continuous variables and compared by clinical comorbidity using Spearman's rank correlation and Wilcoxon rank sum test. Then, the patterns of cytokine responses were investigated and interpreted in the different levels of hyperglycemia and malnutrition.

＊ The abstract, containing the objective, method, result and conclusion should not exceed 300-500words and printed double sided on A4 paper)

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Result :

The clinical characteristics of three groups matched each other except HbA1c, BMI or age. For the current study, 4 cytokines were analyzed and compared among non, mild, and severe DM-TB. All cytokines showed significant differences between non and severe DM-TB. Particularly, IFN-γ showed the apparent elevation under $8.0\% \leqq$ HbA1c in both CD4+ (p=0.006) and CD8+ (p=0.002) T cell responses with Wilcoxon rank sum test. IL-17A had the similar differences between the two groups (CD4+: p=0.026, CD8+: p=0.011). IL-2 was more linear increasing than IFN-γ or IL-17A (CD4+: p=0.008, CD8+: p=0.011). In contrast, IL-10 response was higher in the TB patient within a normal range of HbA1c. In CD4+ T cell response, there were the differences between not only non and severe DM-TB (p=0.002) but also mild and severe DM-TB (p=0.002).

Conclusion :

The current results were compatible with the previous studies, indicating that TB with DM over-enhances Th1 and Th17 type immune responses and reduces Treg response. Assuming the immunosuppressive state due to DM, there is an insight that inflammation is less likely to be induced. However, according to these results, it was estimated that hyperglycemia persisted hypercytokinemia due to the comorbidity up to a certain HbA1c level. Further analysis is warranted to reveal whether the comorbidity of DM and malnutrition affects other cytokine responses such as TNF-α, IL-1β, and IL-6, which have not been found explicit reports.

(499 words)

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