5. A Study of Peripheral Airway Findings Using an Ultrathin Bronchofiberscope and Bronchoalveolar Lavage Flund with Diffuse Panbronchiolitis

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Diffuse panbronchiolitis (DPB) is a clinicopathologic entity characterized by chronic inflammation of the respiratory bronchioles. Since low dose, long term erythromycin treatment has been established as an effective therapy for DPB in Japan the prognosis of most DPB patients has markedly improved. Furthermore, it is considered that roxithromycin and clarithromycin, new 14-member macrolide antibiotics derived from erythromycin, are also effective in the treatment of DPB. However, there is no consensus about the duration of erythromycin treatment for DPB and it is recognized that recurrence can occur after cessation of erythromycin treatment.

We investigated the peripheral airways using an ultrathin bronchofiberscope and bronchoalveolar lavage fluid (BALF) analysis in 10 healthy patients with DPB who were refractory or responsive to macrolide antibiotics and compared them to those from 10 healthy volunteers. The subjects were 10 patients with DPB, 9 males and 1 female with a mean age of 40.3 yrs, all non smokers, and 10 healthy volunteers, 8 males and 2 females with a mean age of 45.7 yrs, all non smokers. The diagnosis of DPB was based on the criteria established by the Japanese Ministry of Health and Welfare. The 10 DPB patients were divided into responsive individuals (5 males, mean age 40.0 yrs) and those refractory to macrolide antibiotic treatment (4 males, 1 female, mean age 40.3 years).

All DPB patients received oral clarithromycin at 200 mg/day. The responsive group were treated for an average of 1.02 years and the refractory group were treated for 2.9 years. None of the DPB patients or healthy volunteers were treated with corticosteroids or other antibiotics during the course of the study and none had had a bronchial infection for at least one month prior to ultrathin bronchofiberscopy and BAL.

BAL was performed on all the cases. Briefly the tip of the fiberscope was wedged into the segmental bronchus of the middle lobe, and 150 ml of sterile saline was infused in boluses of 50 ml through the bronchofiberscope, and was aspirated under low suction using a sterile syringe after each installation. After collection of BALF total cell counts and cell differentials were measured and lymphocyte subsets were analysed by two-colored flow cytometry.

The total number of cells was significantly higher in the refractive DPB patients than in healthy volunteers or in the responsive DPB patients. The percentage and total number of neutrophils was higher, while the percentage and total number of macrophages was lower in the refractory patients than in healthy volunteers or the responsive DPB patients. The percentage of lymphocytes was not significantly different among the three groups but the mean absolute number of lymphocytes was higher in the refractory patients compared to the other two groups. The percentage of $CD4^+$ cells was lower and the percentage of $CD8^+$ cells higher in the refractory patients compared with healthy volunteers or responsive patients. In addition, the CD4/8 ratio was lower in the refractory patients compared to the healthy volunteers.

There was no significant difference in the percentage of $CD3^+CD56^+$ cells (NK cells) or $CD4^+CD29^+$ cells (memory cells) among the three groups however the percentage of $CD8^+S6F1^+$ cells (activated cytotoxic T cells) was higher in refractory DPB patients than in healthy volunteers or responsive DPB patients. Furthermore, the percentage of these cells was also higher in DPB responsive patients than in healthy volunteers.

In refractory DPB patients total cell counts were markedly increased, suggesting that local continuous inflammation still existed despite low dose macrolide treatment. In addition, the decrease in

CD4/CD8 ratio in the refractory patients suggests that $CD8^+$ cells, are involved in the pathogenesis of DPB.

The percentage and absolute number of CD8 cells were higher in refractory DPB than responsive DPB or healthy volunteers. Furthermore, the percentage of cytotoxic T cells increased, which suggests that $CD8^+$ cells, especially cytotoxic cells, are deeply associated with the formation of the pathophysiology of DPB. And in responsive DPB, the percentage of CD8 cells or cytotoxic T cells are lower than in refractory DPB, but still higher than in healthy volunteers.

To observe the peripheral airway changes we performed alveolar bronchography. There were no abnormal ariway findings in responsive DPB. On the other hand, there was bronchectosis and peripheral airway narrowing obstruction in DPB, which suggests that the effect of macrolide treatment was poor in such progressive slides.

In the 10 healthy volunteers there was normal bronchial mucosa to the 13th level of bronchial branches, whereas, in the refractory DPB patients the peripheral airways from the 6th～10th level of bronchial branches showed bronchectosis and there was obstruction at the 11th～12th level of bronchial branches. In addition, secretions in the bronchial lumen were continuously observed from the 5th～6th order bronchi to the 11th-12th level of bronchial branches. In contrast, obstruction to the 11～12th level of bronchial branches could not be observed in responsive patients however, secretions in the bronchial mucosa, especially at the 11th～12th level of bronchial branches, still remained in all the bronchial branches studied.

In conclusion, we have shown the peripheral airway findings in DPB patients obtained using ultra thin bronchofiberscope. In refractory DPB patients obstruction around the 11th～12th bronchial level appeared to be associated with the accumulation of cytotoxic T cells and neutrophils in the peripheral airways. It appeared that macrolide therapy could only acheive symptomatic improvement in progressive DPB patients and if low dose macrolide therapy is not effective for progressive DPB, another therapy, such as steroid therapy of immunosuppressive therapy, should be considered.

Dr. Keicho: We have covered so far DPB in terms of simple observations of bronchofiberscopy, lymphocyte subpopulations and macrolide treatment. Different from the last three presentations, we are going to the genetic predisposition to panbroncheolitis.

6. Genetic Predisposition in Diffuse Panbronchiolitis

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The incidence of DPB is greatest in East Asia. While environmental factors or some other exogenous agent may play a role in predisposition, we have hypothesized that susceptibility may be due to a genetic predisposition unique to East Asia. Recently Dr Sugiyama and his coworkers have reported that the HLA-Bw54 antigen is frequently seen in patients with DPB. Interestingly, this HLA antigen is distributed mainly in East Asia. This finding raises two possibilities for the linkage of this HLA antigen with disease susceptibility. The HLA B gene itself may be important in the pathogenesis of the disease or the HLA haplotype may be just a marker for disease susceptibility and the HLA B gene is linked to the true susceptibility gene.

DNA was collected from 76 patients with DPB and the relationship between HLA and DPB was