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Historical changes in epidemiology of diffuse panbronchiolitis

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Abstract. *Background and objective:* Japanese pulmonologists, experienced in treating patients with diffuse panbronchiolitis (DPB) prior to the 1980s, have uniformly observed that new incidences of DPB are now a rare event in Japan. However, there is no epidemiological data to support this observation. We examined epidemiological trends of the number of patients with DPB in a large company. *Design:* The computerized health records of JR East Company employees were used to identify patients with DPB and then these were followed up using the assessments of these patients in JR Tokyo General Hospital and two other JR hospitals. The whole study period was 27 years (1976-2003), although detailed analyses were carried out for three specific periods; the first was 1976-1980, the second was 1989-1993, and the third was 1999-2003. *Results:* In the first period, 11 DPB cases (four incidence, and seven prevalence) were detected among a total of 355,572 workers. In the second period, three DPB cases (one incidence, and two prevalence) were identified from a total of 180,359 workers. In the third period, no case was found in a total of 144,485 workers. *Conclusion:* This epidemiological trend suggests that both the incidence and prevalence of DPB may have decreased. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 19-25)*

Key words: diffuse panbronchiolitis, epidemiology, incidence, prevalence, BMI

Introduction

In 1969, Yamanaka et al. reported diffuse panbronchiolitis (DPB) for the first time as a disease characterized by numerous micronodular pulmonary lesions composed of chronic inflammatory cells infiltrating the walls of the respiratory bronchioles (1). DPB has since come to be internationally accepted as a disease entity.[2] At the time of its discovery, DPB had a poor prognosis because of recurrent respiratory infections leading to respiratory failure. Since 1985, when long-term, low-dose erythromycin (EM) therapy was introduced, the prognosis of DPB has markedly improved (2, 3). In addition, most Japanese pulmonologists with experience in treating patients with DPB prior to the 1980s have anecdotally noted a decrease in the appearance of DPB, al-

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though no epidemiological survey has yet been done. Therefore, we examined the incidence of the number of patients with DPB over the past 30 years in a relatively large Japanese company.

Methods

The clinical outpatients records from Japan Railway (JR) Tokyo General Hospital along with Sapporo, and Sendai JR hospitals were analyzed. In addition, computerized health records from 1972 of the male population of JR East Company employees were evaluated (most employees were men). These employees had undergone an annual health check which included height, weight, chest X-ray, audiometry, visual testing, and a medical interview by public health nurses of the JR East Health Promotion Center. Compliance with the annual check-ups remained, for a long period of time, as high as 99%. Any employees with long-term nasal and respiratory symptoms, and/or X-ray abnormalities on the annual health check-ups were sent to JR Hospitals for further examination. JR East health records were available from 1972 to assess health findings from the time of initial employment. The study covered 27 years (1976-2003), although detailed analyses were limited to the following three periods: the first was 1976-1980 and with a total of 355,574 examinees, the second was 1989-1993 with 180,359 subjects, and the third period was 1999-2003 with 144,485 examinees. All employees had undergone health check at employment, and passed it except for extremely sick, visual impairment and difficulty in hearing. There is no difference in the economical or familial background among the study population.

Study profiles

In the first and second periods, a DPB diagnosis was based on the initial clinical criteria established by Homma and Yamanaka in 1969 (1). In the third period, the 1998 revised criteria developed by the Ministry of Health and Welfare of Japan (Table 1) were adopted. The main difference between the two sets of criteria is that, in the revised set, chest CT scans are included for radiographical evaluation to detect centrilobular granular shadows. The revised criteria may exhibit greater sensitivity for detecting patients with DPB than the initial criteria. We reapplied the revised criteria to the cases of DPB diagnosed in the first and second periods. As a result, all DPB diagnoses based on the initial clinical criteria were found to meet the requisite for diagnosis with the revised criteria.

Table 1. Diagnostic criteria proposed in 1998 according to the Ministry of Health and Welfare of Japan

Indispensable signs
1. Symptoms: chronic cough, sputum, and dyspnea on exertion.
2. Past history or coexistence of chronic sinusitis
3. Chest radiographic findings: bilateral diffuse small nodular shadows on a plain chest
4. X-ray film or diffuse centrilobular nodular shadows on chest CT images.

Reference signs
1. Physical signs: coarse crackles, sometimes with rhonchi, wheezes or squawk, on auscultation of the chest.
2. Pulmonary function tests and blood gas analysis: FEV_1 < 70% and PaO_2 < 80 mmHg.
3. Elevated titers of cold hemagglutinin

- *Definite cases* should fulfill three indispensable criteria with at least two of the three reference criteria.
- *Probably definite cases* should fulfill three indispensable criteria.
- *Possible cases* should fulfill 1 and 2 of indispensable criteria.

Statistical analysis

We determined the incidence and prevalence of DPB in three 5-year periods (1976-1980, 1989-1993, and 1999-2003), and calculated the age-adjusted incidence rate with the direct method using a standard model population in 1985. Body characteristics were calculated as mean = SD for continuous variables, and two-sample t tests were performed to analyze differences between DPB patients and controls. Analysis of variance was performed to compare the time-dependent changes of prevalence rate in DPB. This was followed by McNemar test (with Yates' revised) and a post hoc Bonferroni's multiple-comparison test. P values less than 0.05 were considered to be statistically significant.

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Results

Incidence and prevalence rates

The clinical course of detected DPB cases are shown in Fig. 1. According to medical interviews, most patients with DPB had a long period of respiratory prodromal symptoms, including nasal discharge or obstruction indicating chronic sinusitis. The longest such period was 29 years, in case #12, followed by 25 years in case #2, 8~14 years in six cases, 1~3 years in four cases, and no such period in case #9. Cases #5 and #13 were excluded in part from the statistical analysis because data before the first period were missed.

The incidence and prevalence of DPB each year during the study period are shown in Table 2. The numbers of prevalence cases are affected by a number of factors including, retirement, death, moving to other hospitals, and missing. In the first period, 11 cases (incidence of four, and prevalence of seven) were observed among 355,572 workers. In the second period, three cases (incidence of one, and prevalence of two) were observed among 180,359 workers. In the third period, no case of DPB was detected among 144,485 workers. Overall, the incidence was three cases in 1976, one case in 1977, and one in 1990. The incidence was zero after 1977 except for one case in 1990.

Incidence and prevalence rates for DPB are shown in Table 3. The incidence rate was 1.12 per 100,000 in the first period, 0.55 in the second period, and 0 in the third period. The age-adjusted incidence rate was 0.88 per 100,000 in the first period, 0.28 in the second period, and 0 in the third period. The prevalence rate was 13.78 per 100,000 in the first period, 6.63 in the second period, and 0 in the third period (this was despite DPB being more widely detected by chest CT scan in the third period). Considering the progress of radiographical evaluations, these findings suggest that the incidence of DPB has decreased with time since 1976 in the JR East Compa-

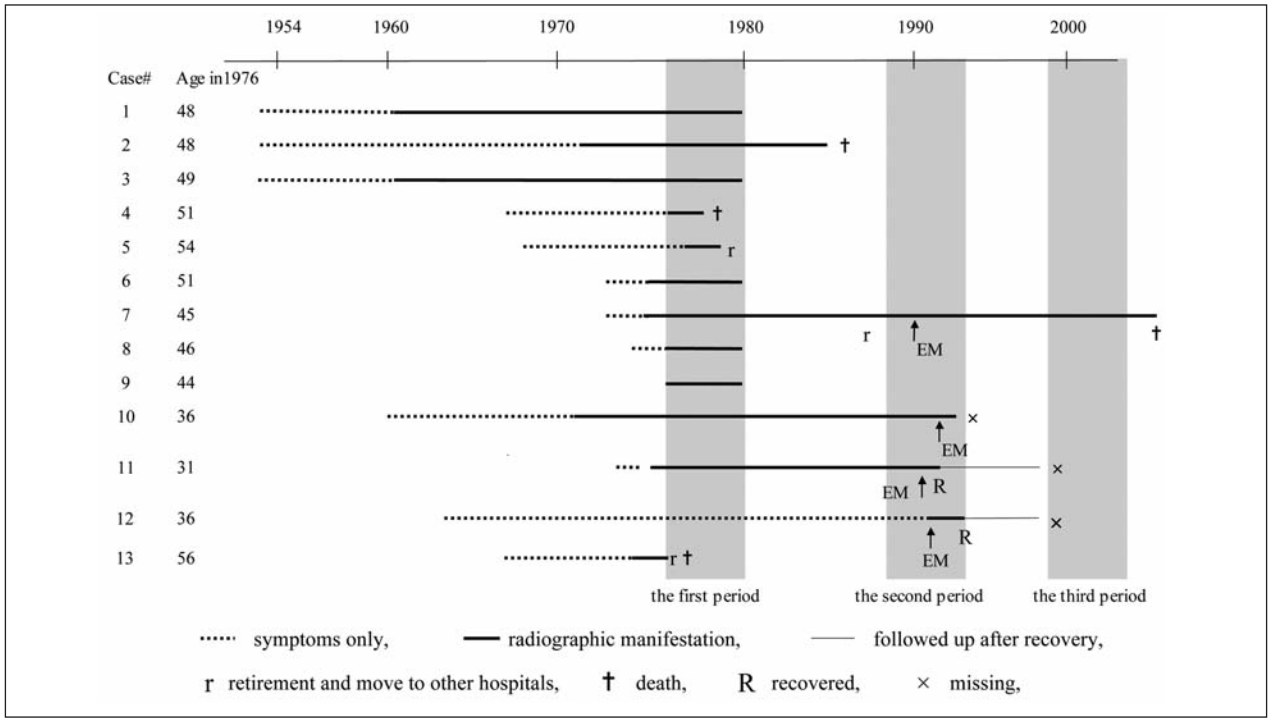

Fig. 1. Clinical course of detected diffuse panbronchiolitis (DPB) cases. This figure shows the progress of all the DPB cases. We could not follow all of their courses completely, because most cases moved to another hospital, or were missing after retirement, and some data between 1981 and 1988 were not available. Only case #2 and #7 could be followed completely. Case #13 was not counted in the first period because of his retirement. Case#10 and #11 discontinued their attendance at our hospital. Case #12 moved to another hospital due to a transfer

Table 2. The number of incidence and prevalence cases in each year

	The first period					The second period					The third period				
	1976	1977	1978	1979	1980	1989	1990	1991	1992	1993	1999	2000	2001	2002	2003
Incidence cases	3	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Prevalence cases	10	11	10	9	9	2	3	3	3	1	0	0	0	0	0

Table 3. DPB crude incidence rates and annual average prevalence rates

	Incidence rate (10^{-5})	Prevalence rate (10^{-5})
The first period (1976~1980)	1.12	13.78
The second period (1989~1993)	0.55	6.63
The third period (1999~2003)	0	0

ny. Time dependent changes of prevalence rates in DPB, was followed by McNemar test (with Yates' revised) and a post hoc Bonferroni's multiple-comparison test, which were p=0.045 and p=0.039 (period I/II), p=0.133 and p=0.125 (period II/III).

Patient physique before onset

The height and body mass index (BMI) of DPB patients was examined before onset, and the BMI of DPB patients was compared with age- and job-matched controls. We hypothesized that a small physique was associated with the onset of DPB. According to medical interviews, three DPB patients had only slight prodromal symptoms that passed the employment health check-up as having no abnormal medical conditions. Height and weight data in 1954 were obtained from the JR East Health Promotion Center. Ten patients were compared with 30 controls in the first period. For these ten cases (cases #1-9, and #13), 30 age- and job-matched controls were chosen at random from male employees in 1976. Height, weight, and BMI are presented in Fig. 2. The mean height of DPB patients was 158.6 ± 4.7 cm, while that of the 1976 controls was 161.5 ± 6.9 cm, in 1976 (p>0.05). There was no change between 1954 and 1976. In 1954, the mean BMI of the patients tended to be lower (19.5) than that of the controls (20.7), although it was not significant in statistical analysis (p>0.05).

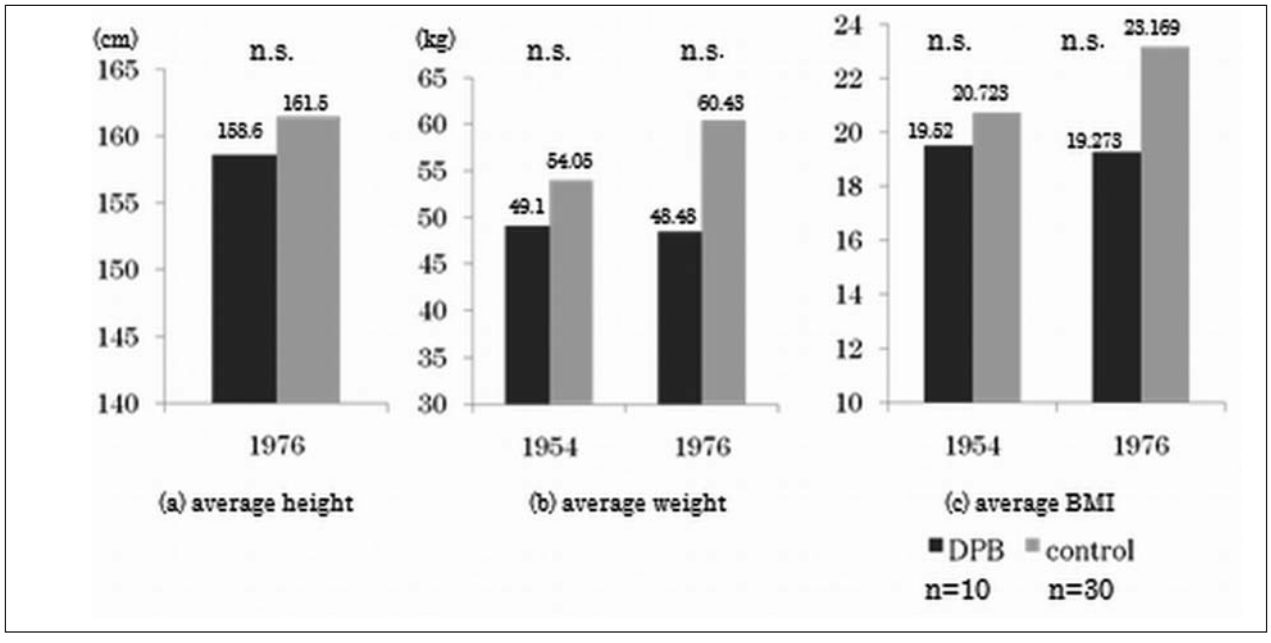

Fig. 2. Body characteristics in diffuse panbronchiolitis (DPB) patients. The average height, weight, and BMI of DPB patients tended to be lower than the controls in 1976, affected by DPB incidence or prodrome. The average BMI of DPB patients tended to be lower than controls, as of 1954; about 20 years before onset of the disease. n.s. ; not significant

Discussion

Very few epidemiological studies of DPB have been available, other than that by Saitoh et al., who performed case-control studies on the occurrence of DPB in 1982 (4). The findings of the present study indicate that the incidence and prevalence rates of DPB have decreased in the JR East Company.

In the small number of incident cases in the present study, it would be difficult to consider that the described clinical pattern and its trend are representative of the overall situation in Japan. However, the study population included around sixty-eight thousands individuals without unusual medical conditions at the time of their employment. Therefore, our findings may contribute to determine the prevalence of DPB in our country, and may also be invaluable in revealing the time when prodromic symptoms and X-ray abnormalities first appear. It is unclear in daily clinical practice when DPB patients first develop abnormal chest X-ray findings.

Homma collected more than 1,000 cases of probable DPB, and 82 histologically confirmed cases, through a nation-wide survey from 1978-1980. They noted that secondary ectasia of proximal bronchioli probably occurred in the advanced stage of DPB (5). We also observed these findings in case #7, in which typical centrilobular granular shadows were initially noted, with progression to diffuse, ring-shaped shadows indicative of diffuse bronchiectasis (Fig. 3). Secondary ectasia of proximal bronchioli seemed to occur in the advanced stage of DPB. Cases with diffuse bronchiectasis similar to case #7 are thought to progress from DPB.

Although the etiology of DPB remains unknown, the participation of genetic factors was sug-

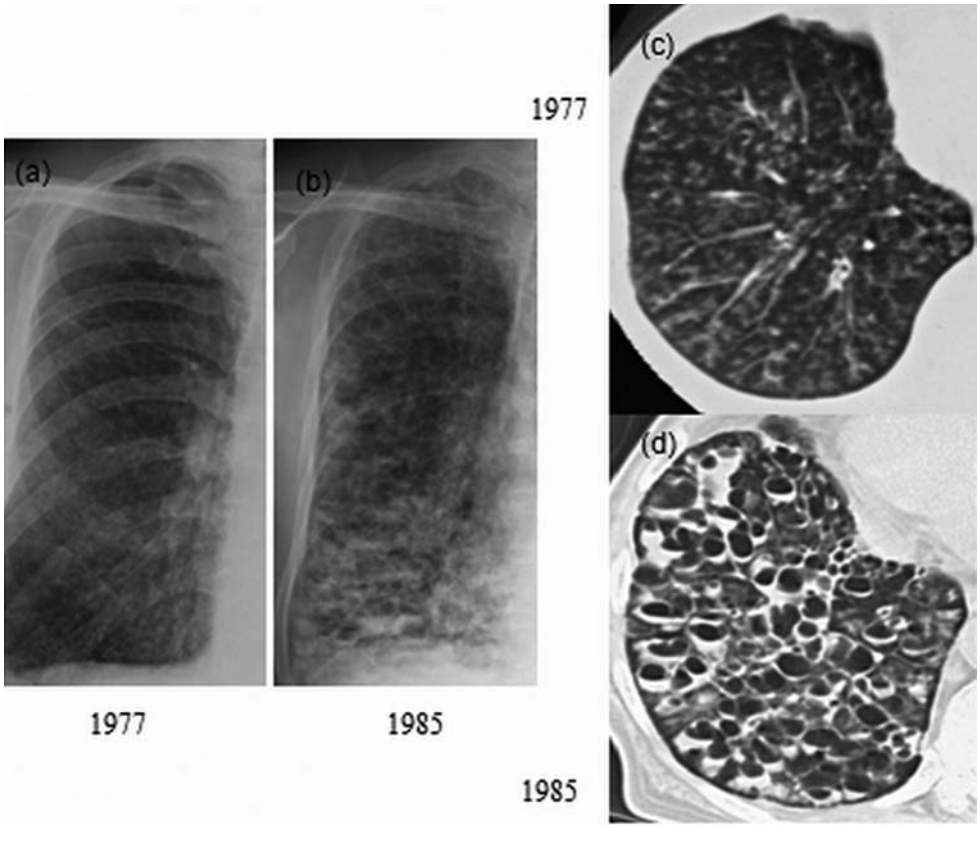

Fig. 3. Chest X-ray and CT findings in Case #7 (a) Chest X-ray and (c) CT in 1977 showing diffuse centrilobular nodules. (b) Chest X-ray and (d) CT in 1985 progressing to diffuse bronchiectasis

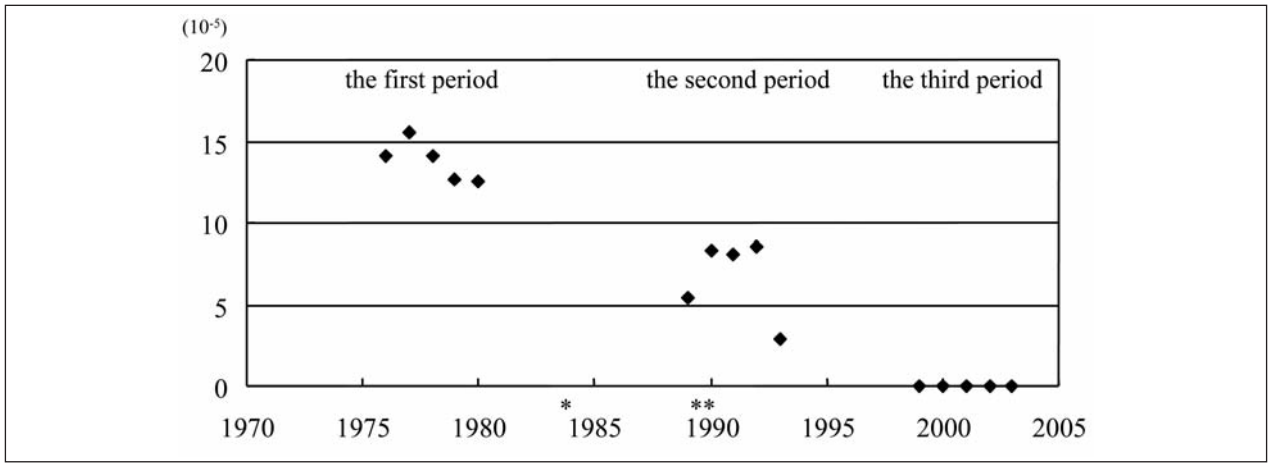

Fig. 4. Time-dependent changes of prevalence rates in diffuse panbronchiolitis (DPB). Macrolide therapy was introduced for DPB between the first and second period, and was introduced for chronic sinusitis in the second period. *1984, first report of macrolide therapy for DPB. **1990, first report of macrolide therapy for chronic sinusitis

gested by Keicho and coworkers. They found that the major disease-susceptibility gene for DPB exists between the two HLA loci on chromosome 62 (6). However, not all DPB patients have genetic disorders and not all individuals with genetic disorders have DPB, suggesting that non-genetic factors may also play a role in the aetiology of this condition.

Differences in diet and environment may contribute to the development of DPB. It could also be that small physique is associated with DPB. In comparison of BMI between DPB patients and controls in 1954, we found that the mean BMI of DPB patients from 1954 tended to be lower that that of the controls. In present study, it was not significant in statistical analysis between the BMI of the patients and that of the controls. We estimate that few number of the patients would lead it. According to medical interviews from ten DPB patients, seven had no prodromal symptoms and three had only slight prodromal symptoms that passed the employment health check-up as a normal medical condition. This suggests that DPB patients had smaller physiques compared with controls 20 years prior to the onset of DPB.

Although adult height is genetically determined, it may be influenced by diet in childhood and adolescence (7). Adult height has been used as a proxy indicator of nutrition early in life in relation to subsequent risk of incidence and mortality from chronic respiratory disease. Although it is possible that a gene involved in the onset of DPB is linked to another gene involved in height determination, we found no evidence to support this hypothesis. According to Japanese Health and Welfare statistics, mean height for men in their 40's was 162.9 cm in the first period, 166.4 cm in the second period, and 168.8 cm in the third period (this increase being the result of improved nutrition in Japan). Although the reason for the relationship between DPB and malnutrition is unclear, chronic periodontal disease due to malnutrition may result in the release of cytokines such as IL-1 and TNF-α, which may stimulate respiratory epithelial cells (8). It may thus be that the release of cytokines due to malnutrition causes chronic respiratory diseases such as DPB. Furthermore, the bronchial mucosa become fragile as a result of malnutrition in childhood, since the growth of bronchi continues until about eight years of age. We speculate that improved nutrition suppresses the onset of DPB. A further epidemiological study of the prevalence of chronic sinusitis or prodromal symptom of DPB is required.

Since the efficacy of long-term, low-dose EM therapy in patients with DPB was reported in 1984 (2, 3), the prognosis of DPB has dramatically improved. In the 1970s, prior to the introduction of EM therapy, the overall 5-year survival rate was 62.9%. Between 1980 and 1984, the survival rate was still limited to 72.4%, but after 1985, when EM therapy was introduced, the 5-year survival rate improved significantly to 91.4% (4). New applications of 14-membered ring macrolides, including EM,

clarithromycin and roxithromycin were reported, and these agents proved to be effective, not only for DPB, but also for various chronic respiratory disease such as bronchiectasis and chronic sinusitis.

Macrolides therapy were effective in many DPB patients except for secondary diffuse bronchiectasis, advanced stage in DPB. They were introduced to DPB therapy between the first and second period of our study; and for the treatment of chronic sinusitis in the second period. It appears that patients with a mild degree of DPB improved between the first and second periods. Also since chronic sinusitis prior to the development of DPB could be treated between the second and third periods, the incidence rate of DPB decreased (Fig. 4). In addition, most DPB cases complicated with chronic sinusitis were treated with macrolides, and were thus dramatically improved by this treatment. Thus, we anticipate that treatment for chronic sinusitis may be a preventive treatment for lower respiratory tract inflammation and may explain the decreased incidence of DPB after the introduction of macrolide therapy.

Our findings indicate that incidence and prevalence rates of DPB have decreased over time in a large Japanese working population. Small physique may possibly be associated with the development of DPB, and long-term, low-dose EM therapy, at an early stage, could decrease the prevalence rate of DPB.

Acknowledgements

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