Diffuse Panbronchiolitis

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Diffuse Panbronchiolitis (DPB), as distinguished from so called COPD (bronchial asthma, chronic bronchitis and chronic pulmonary emphysema), bronchiectasis or alveolitis, has been noted since 1966 in Japan. Through clinical, radiologic, physiologic and pathologic analysis based on accumulated data by Homma and Yamanaka, a nationwide survey with the cooperation of 30 universities, national and municipal institutions throughout the country was organized in 1980 to investigate the incidence and the morbidity of the disease under the aid of the Ministry of Health and Welfare of Japan. The results obtained by this project team during 1980 to 1982 disclosed the features of clinical and pathological findings, the gist of which was already reported. As stated later, DPB is associated with HLA-Bw54 antigen which is found specifically in Japanese and Chinese and not in Caucasians, suggesting that DPB may be an ethnically specific disease.

1. The description of the disease

DPB is a chronic inflammation situated mainly in the respiratory bronchioles, present diffusely in both lungs and causing severe respiratory disorder. The lesions are composed of respiratory bronchiolitis and peribronchiolitis.

The name, diffuse panbronchiolitis, was given to this disease by Yamanaka, head of the Department of Pathology, St. Luke’s International Hospital. The word “Diffuse” means, of course, diffuse scattering of extensive lesions in both lungs, the word “pan-” is used in the same sense as pan- of panvasculitis, as the wall of the respiratory bronchiole is thin and the lesion extends easily to the whole layer. This bronchiole means a respiratory bronchiole, and not a non-respiratory bronchiole of the airway system.

2. Epidemiology

The nationwide study revealed that cases with DPB are distributed from the northernmost to the southernmost districts of Japan.

1) Age of onset: The age of onset is from the teens to the ninth decade in both sexes and the age of initial examination increases gradually after middle age.

2) Sex ratio: Male to female ratio is about 1.4 to 1, but considering the rate of those examined, there seems no essential difference due to sex.

3) Smoking: No close relationship with the habit of smoking is noted.

4) Complication: 84.8% of the cases have or once had chronic paranasalitis. It must be emphasized that this is one of the characteristics of DPB. Incidence of chronic paranasalitis in patients’ families is 20.0%.

5) Diagnosis prior to admission: Chronic bronchitis (30.4%), Bronchiectasis (26.2%), and Bronchial asthma (24.2%) are most frequently suspected or diagnosed.

2. Pathology

The features of pathological findings are summarized as follows (Figure 1 and 2):

1) The lesions diffusely distribute in bilateral lungs and are exclusively located in the respiratory bronchioles.

2) Peripheral alveoli distal to the lesion are intact.

3) Thickening of the walls of respiratory bronchioles with infiltration of lymphocytes and plasma cells. The narrowings of the bronchioles are caused by round cell infiltration or edematous
Fig. 1. Macroscopic appearance of cut surface.

Fig. 2. Microscopic appearance.

granulation tissues.

4) Cicatricial narrowing and constriction of the respiratory bronchioles with proliferation of granulomatous tissues and accumulation of foamy cells within the wall and neighboring area in later stage.

5) Secondary ectasis of the proximal terminal and nonrespiratory (airway) bronchioles.

6. Clinical pictures

1) Initial symptoms and the mode of onset:
Initial symptoms are shortness of breath, cough and small amount of tenaceous sputum, frequently accompanied by wheezing. Early occurrence of hypoxemia is not unusual. Mode of onset is usually insidious. Sooner or later bacterial pulmonary infection comes up accompanying increased amount of yellowish sputum.

2) X-ray and CT image and Bronchography:
Miliary or fine nodular dissemination in both lung fields is characteristic picture, often accompanied by hyperinflation which makes the dissemination difficult to be seen. Bronchogram frequently shows slight secondary dilatation of the terminal bronchioles which indicate the obstruction of the respiratory bronchioles.

Schematic classification of X-ray findings is presented in Figure 3. CT image is useful to clarify the location of fine nodular lesions. Selective alveolobronchography shows how to occur the secondary bronchiolectasis following the obstruction of the primary lesions.

3) Pulmonary function:
Mixed ventilatory impairment consisted of slight restrictive and marked obstructive disturbance, early hypoxemia later accompanied by hypercapnea and cor pulmonale. The Figure 4
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shows the characteristic of the pulmonary function disorder. The alveoli are in the state of overdistention, but the alveolar walls are not destroyed, kept normal, and pulmonary compliance and diffusion capacity remain within normal range. As the disease progresses, alveolar hypoventilation increases and hypercapnia appears. In the course of many years, it enters the states of pulmonary hypertension, right heart burden and cor pulmonale. Further, as to ventilation, slight restrictive disturbance is noted, as the fibrous tissue proliferates from the respiratory bronchioles to the proximal part. Namely, from the aspect of ventilation it is characterized by a combination of strong obstructive and slight restrictive disturbances. Our cinebronchographical study disclosed the collapse of segmental bronchi during forced expiration.

4) Immunological aspect:

Titers of cold hemagglutinin are generally markedly elevated in patients with DPB. The amount of IgA is also increased in most DPB cases. Analysis of T lymphocyte subsets by OKT series monoclonal antibodies disclosed a significant elevation of the OKT4/OKT8 ratio compared with healthy controls due to increase in OKT4+ and decrease in OKT8+1. These are considered as characteristic features in immunological aspects of DPB.

5) Sputum bacteriology:

Hemophilus influenzae (44%) and Pneumococci (12%) are most often identified in the initial stage, later followed by Pseudomonas superinfection.

Pseudomonas infection, when occurs, is stubborn and incurable, fluctuates but progresses gradually and finally a fatal outcome ensues due to pulmonary insufficiency.

7. Etiology

The etiology of DPB is unknown. However, there have been increasing reports on DPB cases observed in same family. Chronic sinusitis is well known about its high incidence in members of one family. Recent studies on HLA antigens in DPB patients disclosed that HLA-Bw54 was found most frequently in DPB cases (68.4%, X²=36.2, corrected P=2.04x10⁻⁹, relative risk 16.8) compared with controls consisted of 184 healthy persons (11.4%). According to histocompatibility testing, HLA-Bw54 was found specifically in Japanese and Chinese and not in Caucasians (Table 1). Therefore, the above mentioned facts suggest that DPB may be an ethnically specific disease and that there is a gene controlling susceptibility linked with a Japanese-specific HLA antigen.

8. Diagnosis

From the above mentioned morphological changes, X-ray image and pathophysiology, the following diagnosis guide was made. The following principal clinical findings shall be filled in all items. Histologic proof when obtained shall establish the diagnosis. Chronic bronchitis, bronchial asthma and chronic emphysema should be differentiated carefully.

1) Clinical symptoms: cough, sputum, shortness of breath on exertion.

2) Physical signs on the chest: moist (usually crepitant) and dry relays.

3) Chest X-ray findings: diffuse scattered granular shadows in bilateral pulmonary areas, pulmonary hyperinflation.

4) Pulmonary function tests and blood gas findings: Among 4 items, diminution in FEV₁₀₀ % (below 70%), diminution of vital capacity (below 80% of predicted value), increase in residual air above 150% of predicted value) and hypoxemia (below 80 mmHg), 3 or more must be met.

5) Complication: chronic sinusitis.

Table 1. Antigen frequencies for the HLA-Bw 54 in various ethnic groups.

| Ethnic Group   | Bw 54(+) % | No. | Ethnic Group   | Bw 54(+) % | No. |
|---------------|------------|-----|---------------|------------|-----|
| Black         | 218        | 143 | English       | 437        | 0   |
| African       | 184        | 0   | French        | 304        | 0   |
| American      | 6          | 10  | German        | 522        | 0   |
| Case Coloured | 32         | 0   | Hungarian     | 105        | 0   |
| Italian       | 322        | 0   | Hungarian     | 105        | 0   |
| Jewish Ashkenaz      | 122       | 0   | Jewish Non-Ashkenaz | 62       | 0   |
| Japanese      | 110        | 12  | Scandinavian  | 99         | 0   |
| Chinese       | 48         | 10  | Scots         | 35         | 0   |
| Mongoloid     | 379        | 0   | So. African   | 33         | 0   |
| Chinese       | 184        | 0   | Spanish       | 222        | 0   |
| Other         | 262        | 0   | Swiss         | 87         | 0   |
| Other         | 169        | 0   | Yugoslav      | 76         | 0   |
| Caucasian     | 867        | 0   | Other Caucasian| 169       | 0   |
| American      | 184        | 0   | Australian    | 158        | 0   |
| Asian Indian  | 40         | 0   | Australian    | 158        | 0   |
| Mexican       | 42         | 0   | Australian    | 158        | 0   |
| Other         | 76         | 0   | Canadian      | 100        | 0   |
| Czech         | 140        | 0   | Canadian      | 100        | 0   |
| Dutch         | 95         | 0   | Dutch         | 95         | 0   |

Histocompatibility Testing, 1980

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increased IgA, elevation of OKT4/OKT8 ratio (when possible).

7) HLA-Bw54 antigen (when possible).

What must be noted here is, common to any other study on diseases, that cases collected first have all undisputable symptoms and findings, as the disease becomes more widely recognized, early or slight cases can be diagnosed with scanty symptoms or findings and better prognosis are obtained, which are general principles.

9. Prognosis

Missing of early diagnosis and early treatment with corticosteroids may be followed by relentless progressive pulmonary insufficiency accelerated by Pseudomonas pulmonary infection.

A clinical course of one of typical cases is shown in Figure 5. Prognosis after the Pseudomonas aeruginosa superinfection is very poor, namely, 5 year-survival rate is only 8%. Even with laborious treatment, combining various antibiotics, including inhalation, i.e. injection etc, detected bacteria and the amount of sputum may decrease or disappear temporarily, but will appear with aggravated symptoms with gradually increasing difficulty in the control of hypoxemia and hypercapnia and finally a fatal outcome results with respiratory insufficiency.

10. Treatment

The author considers the therapeutic measures to be in 3 stages (Table 2) 19).

In this first stage, the sputum culture is negative. Main symptoms are short breath on exertion and slight cough. If any, the sputum is scanty and mucoserous. Crepitant rales over both lungs, and often wheezing are heard. Blood gas analysis shows hypoxemia.

The treatment for this stage is steroid administration and oxygen inhalation. Steroid administration is aimed at radical cure of this disease, starting with 30 mg daily calculated as prednisolone. The dose is reduced by 10 mg after two weeks, and ends with 5 mg a weeks. Decrease in dosage depends on the disappearance of hypoxemia, i.e. normalization of PaO₂, and improvement in the shortness of breath on exertion. Usually great improvement is observed within one week of treatment. The second treatment, oxygen administration, is a symptomatic
one for hypoxemia and short wind, a flow of 1–2 l per minute is usually adequate. Further, if active parasinusitis is present, it should be treated.

In the advanced second stage, pulmonary infection appears with Hemophilus influenzae and sometimes Pneumococcus, observed clinically by the appearance of colored and increased amount of sputum in addition to wheezing and hypoxemia. The X-ray image helps us to observe the therapeutic course. Wheezing is not paroxysmal as in bronchial asthma, and does not usually appear at midnight or early morning, but characteristically lasts all through the morning, improving in the afternoon. At this time the treatment is first aimed at the aforesaid bacterial infection of the lung, giving antibiotic and expectorant. Combining an expectorant and a bronchodilator for inhalation is also effective. For spastic contraction of the airway the same bronchodilator is used as for bronchial asthma. If pulmonary infection is controlled well, wheezing disappears and, therefore, steroid is not always needed. Oxygen, of course, is given, when needed as a symptomatic therapy.

In the third stage, stubborn and incurable infection of the lung by P. aeruginosa appears predominant, respiratory insufficiency progresses gradually. The treatment at this time consists of the measures for P. aeruginosa infection, spastic contraction of the airway and respiratory insufficiency. Morphological changes include destruction of the respiratory bronchiolar wall, obstruction of the lumen due to cicatricial tissues with deposition of carbon particles and subsequent dilatation of bronchioles proximal to this obstructions. The sputum becomes strongly purulent, increasing to as much as 100 – 200 ml, sometimes 300 ml a day. Hypoxemia becomes severe, and carbon dioxide increases, too. Edema appears, if right cardiac insufficiency develops.

To treat P. aeruginosa infection, there has been an increasing number of effective antibiotics available recently and the treatment has become much easier than before, but even if sputum and P. aeruginosa decrease or disappear temporarily, aggravation often reappears, with long-term recurrence of progression and regression. Bronchodilators and expectorants may be combined as in the treatment in the second stage, but spastic contraction of the airway is severe and intractable in this stage, and the use of steroids cannot be avoided. High concentration of Oxygen administration for hypoxemia may increase carbonic acid gas in this stage, and the concentration should be adjusted constantly, depending on the blood gas analysis values.

The above is an outline of the treatment, but the prognosis becomes poor with the superinfection by P. aeruginosa. So the vaccine therapy is being studied as one of the measures for it. One starts with an injection of minute quantities of original endotoxin protein, protease toxoide, elastase toxoide and exotoxin, and increasing the dose gradually to produce antibodies in the body of the host. This method has two objectives. The first one is to use it in a patient of the aforesaid second stage, i.e. without pulmonary infection by P. aeruginosa in order to prevent P. aeruginosa superinfection. The second is to use it in a patient in the third stage, i.e. with complication of pulmonary infection by P. aeruginosa, to colonization P. aeruginosa and to improve symptoms and findings. At present, the effect is expected to improve the patient’s prognosis.

11. Conclusion

Our present knowledge and treatment of diffuse panbronchiolitis, which is considered an incurable disease of unknown cause have been reported. The best and only method we have today to rescue the patients from this disease is “early diagnosis and early treatment”. Infection by P. aeruginosa is one of the turning-points to a poor prognosis, and conversely as a turning-point to a radical cure. And I’d like to emphasize that interrogation as well as percussion and auscultation findings play the chief roles as ever. There has been an increasing number of papers reporting cases with bronchobronchiolitis obliteratorans (BBO). We classify them into two categories, one of unknown etiology and the other accompanying rheumatoid arthritis. Both of them have obliteration in small bronchi and non-respiratory bronchioles of 1 - 3 mm in diameter and quite different pathology from DPB.
REFERENCES

1) Yamanaka A, et al: The problems in chronic bronchitis and bronchial asthma from pathological viewpoints. Nippon Rinsho 24: 851, 1966.
2) Yamanaka A, et al: The problems in chronic obstructive pulmonary disease: special reference to diffuse panbronchiolitis. Intern Med 23: 442, 1969.
3) Homma H: Diffuse panbronchiolitis. Jap J Thorac Dis 13: 383, 1975.
4) Homma H: Diffuse panbronchiolitis (diffuse respiratory bronchiolitis). Jap J Int Med 65: 644, 1976.
5) Tanimoto H: Clinical picture of diffuse panbronchiolitis. Nippon Kyobu Rinsho 29: 430, 1970.
6) Izumi T: Annual report on the study of diffuse disseminated lung disease (Director H. Homma by Grant-in-Aid from the Ministry of Health and Welfare) P. 3, 1983.
7) Homma H, et al: Diffuse Panbronchiolitis. A Disease of the Transitional Zone of the Lung. Chest 83: 63, 1983.
8) Tanimoto H and Nakata K: Present status of the study on DPB. Igaku-no-Ayumi 121: 257, 1982.
9) Honda K and Nishimura K: CT image and X-ray findings. Medicina 21: 2624, 1984.
10) Maeno H, et al: Selective Alveolo-bronchography in DPB. Bronchology 5: 53, 1983.
11) Araki T, et al: Pulmonary function disorders in DPB and differential diagnosis. Nippon Kyobu Rinsho 42: 1043, 1983.
12) Tanimoto H: Ginebronchography in DPB. Resp. and Circ. 29: 487, 1981.
13) Hirata K, et al: An immunological study in DPB. Nippon Kyobu Rinsho 38: 90, 1979.
14) Sugiyama Y, et al: Levels of cold hemagglutinin in patients with DPB and various respiratory diseases. Respiration 3: 694, 1984.
15) Yoshimura K, et al: Immunological studies on DPB. Jap J Thorac Dis 22: 992, 1984.
16) Suzuki M, et al: Familial cases in DPB. Jap J Thorac Dis 19: 645, 1981.
17) Suzuki H, et al: HLA antigen in Sinobronchial syndrome. J Jap Bronchoesophagol Soc 34: 270 1983.
18) Terasaki PI: Histocompatibility testing 1980. The ULCA Tissue Typing Lab P. 959, 1980.
19) Homma H: Diffuse panbronchiolitis. Asian Med J 25: 665, 1982.
20) Yoshimura K, et al: Use of Pseudomonas aeruginosa multicomponent vaccine in patients with intractable lower respiratory tract infection associated with DPB. Jap J Thorac Dis to be published.