Case Report

Diffuse panbronchiolitis: A case report from a Chinese consanguineous marriage family and literature review

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Abstract
Diffuse panbronchiolitis (DPB) is a chronic diffuse airway inflammatory disease, which is strongly associated with the class I human leukocyte antigen (HLA) alleles. Here, we report a pair of sisters who have been suffering from chronic cough, expectoration and wheezing for many years. They were previously misdiagnosed as chronic bronchitis and bronchial asthma, and were recently diagnosed as diffuse panbronchiolitis. The 36-year-old elder sister suffered from diffuse panbronchiolitis complicated with pulmonary tuberculosis. The 30-year-old younger sister suffered from diffuse panbronchiolitis complicated with bronchial asthma and bronchiectasis. We have performed HLA genotyping research on the two sisters, their parents and younger brother. The results showed that all family members were positive for HLA-A24 and HLA-B13. The younger sister and mother were positive for HLA-A2. The younger brother and father were positive for HLA-A11. We suspect that the two sisters’ disease susceptibility may be caused by their parents’ consanguineous marriage. In this study, we reported the clinical characteristics of the two sisters with diffuse panbronchiolitis and shared the associated HLA genotyping results of this family cluster, hoping to provide reference for the etiology, diagnosis and treatment of this disease.

Keywords
Diffuse panbronchiolitis, DPB, clinical characteristics, HLA genotyping, consanguineous marriage

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Introduction
Diffuse panbronchiolitis (DPB) is a distinctive chronic progressive pulmonary disease with unknown pathogenesis and characterized by chronic inflammation in respiratory bronchioles and sinobronchial infection.¹ It is a rare complex genetic disease that mainly affects East Asians and is strongly associated with the class I human leukocyte antigen (HLA)-B54 in Japanese and HLA-A11 in Koreans.² This uneven distribution is suspected to be highly associated with genetic predisposition located between HLA-A and HLA-B loci. More than 80% of the patients have chronic sinusitis, which usually precedes the lower respiratory tract symptoms by years.³ If left untreated, DPB will progress to bronchiectasis, respiratory failure, and eventually death.⁴ Here, we have reported a

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pair of sisters with diffuse panbronchiolitis and conducted HLA-A and HLA-B genotyping on them and their families. We hope that our cases report can provide reference for the diagnosis and treatment of this disease, and hope that our HLA high-resolution genotyping research will also be helpful to clarify its etiology and pathogenesis.

Methods

The study was performed in Affiliated Hospital of North Sichuan Medical College. The written informed consent from all cases involved was obtained before enrollment. 5 ml of whole blood (EDTA anticoagulant) was collected from all cases. Genomic DNA from whole blood samples was used for next generation sequencing (NGS) HLA typing. DNA concentration greater than 50 ng/ul. The ratio of OD260/OD280 was between 1.7 and 1.9.

The NGSgo-AmpX kit was used to amplify the HLA-A and HLA-B loci. Amplicons were pooled and fragmented enzymatically using NGSgo-LibrX kit. Then “barcode” adapters were ligated on specimen with NGSgo-IndX kit, according to the NGSgo workflow. The pooled library was sequenced by a MiniSEQ instrument (Illumina), using paired-end sequencing. FASTQ files were assembled and analyzed with NGSEngine (version 2.10, GenDx). The operation steps were carried out according to reagent instructions. Genomic DNA kit, NGSgo-AmpX kit, NGSgo-LibrX kit, and NGSgo-IndX kit were purchased from GenDx Company, USA.

Case presentation

Case 1

A 36-year-old female patient was admitted to our hospital due to chronic cough, expectoration, chest tightness and wheezing. She is a never smoker. She had experienced chronic sinusitis since the age of 12 and started experiencing cough and purulent sputum at the age of 20. The symptoms progressively worsened, presenting with exertional dyspnea and constant wheezing. At the age of 25, the patient underwent “thoracotomy drainage and biopsy” in the local hospital due to “empyema and pleural effusion.” Physical examination on admission revealed diffuse expiratory wheezes and coarse crackles in both lungs. Pulmonary function test showed that the ratio of the forced expiratory volume in 1 second to the forced vital capacity (FEV1/FVC) was 43.39% (Table 1). Blood gas analysis showed hypoxemia with an oxygen partial pressure (PaO2) of 62 mmHg and oxygenation index of 155 mmHg. Chest high-resolution computed tomography (HRCT) scan showed well-defined multiple centrilobular nodules and diffuse tree-in-bud pattern (Figure 1A). No obvious abnormalities were found in routine blood tests, procalcitonin, sputum smear microscopy, sputum culture, tuberculosis bacilli gamma interferon release test, rheumatoid factors, humoral immunity, connective tissue related antibodies, anti-neutrophil cytoplasmic antibody, etc. On the first admission, the patient’s symptoms improved after symptomatic treatment such as antitussive, expectorant and antiasthmatic treatment and discharged from the hospital automatically.

However, the patient presented with the above symptoms repeatedly and was hospitalized in our hospital again after 1 month. On this admission, we performed further investigations on this patient. Paranasal sinus CT showed bilateral maxillary sinus inflammation (Figure 2A, 2B). Cold agglutinin level was in the normal range. A diagnosis of diffuse panbronchiolitis was made given the symptoms, signs, history of sinusitis, radiological, pulmonary function and laboratory findings. In this hospitalization, we treated the patient with azithromycin (500 mg per day), and the respiratory symptoms of the patient were obviously improved. However, dyspnea

Table 1. Pulmonary function results of the case 1 and case 2.

| Case NO. | Time              | FEV1 (%Pre) | FVC (%Pre) | FEV1/FVC (%) | FeNO |
|---------|------------------|-------------|------------|--------------|------|
| 1       | First admission  | 0.61 L (23.5%) | 1.41 L (47.0%) | 43.39 | NA  |
|         | 17 months later  | 0.66 L (25.8%) | 1.35 L (45.3%) | 49.09 | NA  |
|         | 26 months later  | 0.59 L (22.3%) | 1.42 L (46.3%) | 41.49 | NA  |
| 2       | First admission  | 1.42 L (53.0%) | 2.60 L (84.0%) | 63.00 | 13 ppb |
|         | 25 months later  | 1.51 L (56.7%) | 2.76 L (89.6%) | 54.78 | NA  |

%Pre, Percentage of reference value to predicted value. FeNO, fractional exhaled nitric oxide. NA, not available.
symptoms of the case 1 were not well controlled, so we treated the patient with prednisone acetate for 12 months. The dose was gradually reduced from 30 mg to 10 mg per day and finally stopped.

Since then, the patient has been followed up at our hospital for 2 years, sometimes hospitalized for deterioration of her condition. Sixteen months after the definite diagnosis, the patient was hospitalized again in our hospital for cough, expectoration and dyspnea. Chest CT showed a small nodule at the upper tip of the right lung (Figure 3D). Sputum culture showed a small amount of Pseudomonas aeruginosa growth (++).

Fiberoptic bronchoscopy revealed abundant purulent secretions in the left and right main bronchi and all levels of bronchi (Figure 4). Bronchoalveolar lavage fluid culture showed that Pseudomonas aeruginosa was 300 colony-forming units per milliliter (CFU/ml). The second bronchoscope lavage fluid smear revealed 1 root of acid-fast bacilli/300 visual field, and the culture showed a small amount of fusarium. Mycobacterium tuberculosis complex group DNA was positive. The patient was diagnosed as secondary pulmonary tuberculosis and received antituberculosis treatment with isoniazid, rifapentine, ethambutol and moxifloxacin. Since then, the patient has received anti-tuberculosis treatment for up to

Figure 1. Chest CT findings of the case 1. Chest CT showed bilateral diffuse small nodular shadows which presented with typical tree-in-bud pattern. Figure 1(A), 1(B), 1(C), 1(D), 1(E), 1(F) are the chest CT of the patient at the first diagnosis, 2 months, 4 months, 16 months, 18 months and 26 months later, respectively.

Figure 2. Paranasal sinus CT findings of case 1 and case 2. Figure 2A and 2B are sinus CT of case 1. Figure 2C and 2D are sinus CT of case 2. Inflammatory lesion of maxillary sinus (red arrows). Inflammatory lesion of ethmoid sinus (blue arrow).
12 months. The patient’s condition gradually improved and the nodule in the right lung showed significant shrinkage (Figure 3E, 3F) after anti-tuberculosis treatment.

**Case 2**

This patient is the younger sister of the above patient. She is a 30-year-old female who was admitted to our hospital due to persistent cough, expectoration, hemoptysis and dyspnea. The patient began to suffer from recurrent cough and hemoptysis at the age of 15. She started experiencing productive purulent sputum at the age of 20, and the amount of sputum increased year by year. The above-mentioned symptoms occurred repeatedly and progressively worsened, presenting with exertional dyspnea at the age of 24. Case 2 had recurrent episodes of wheezing, chest tightness and cough, especially after exposure to cold air, pungent odor and exercise. The wheezing sound can be heard in both lungs during an attack. Pulmonary function result from a local hospital showed an FEV1/FVC ratio of 63% and a positive bronchodilation test (FEV1 increased by ≥12% and ≥200 ml in absolute value after inhalation of β2 agonists such as salbutamol). In 2010, she was diagnosed with bronchiectasis and asthma in the local hospital. Treatment with budesonide and
formoterol fumarate powder for inhalation (160 ug, twice a day) did not lead to any improvement, thus leading to admission to our hospital for further examination and treatment.

Like her elder sister, she suffered from chronic sinusitis from childhood. Physical examination on admission revealed diffuse expiratory wheezes and coarse crackles in both lungs. Pulmonary function test showed that FEV1/FVC was 63.0% (Table 1). Blood gas analysis showed hypoxemia with PaO$_2$ of 75 mmHg and oxygenation index of 187.5 mmHg. Chest CT showed bronchiectasis and diffuse small nodules in both lungs (Figure 5). Paranasal sinus CT showed bilateral maxillary sinusitis and ethmoid sinusitis (Figure 2C, 2D). Cold agglutinin level was in the normal range. Other relevant examinations such as routine blood tests, procalcitonin, sputum smear, sputum culture, bronchoscopy, tuberculosis screening,

Figure 5. Chest CT findings of the case 2. Chest CT showed bilateral diffuse small nodular shadows and bronchiectasis. Figure 5(A, G), 5(B, H), 5(C, I), 5(D, J), 5(E, K), 5(F, L) are the chest CT of the patient at the first diagnosis, 1 months, 3 months, 8 months, 16 months and 25 months later, respectively.
etc. showed no obvious abnormalities. In view of her symptoms, signs, history of sinusitis, chest imaging, pulmonary function and laboratory findings, we have confirmed her diagnosis of diffuse panbronchiolitis. We treated the case 2 with azithromycin (500 mg per day) and prednisone acetate (30 mg per day), and the respiratory symptoms of her were obviously improved. However, the case 2 developed diarrhea during the use of azithromycin and did not take macrolide drugs regularly, resulting in her repeated condition and difficulty in recovery.

The two sisters grew up in different living environments, but they had similar manifestations of diffuse panbronchiolitis. More importantly, we learned that their parents are cousins, and their disease susceptibility may be attributed to their parents’ consanguineous marriage. Therefore, we conducted HLA genotyping tests on the two sisters, their parents and brother. The results revealed that the case 1 and case 2 were negative for HLA-A11 and HLA-B54, but the father and younger brother were positive for HLA-A11 (Table 2). Therefore, we performed chest CT and sinus CT examination on the father and brother. The results showed no obvious abnormalities in their chest CT, but father’s sinus CT showed bilateral maxillary sinus inflammation (Figure 6B).

**Discussion**

DPB is a progressive inflammatory airway disease characterized clinically by a chronic cough, sputum, exertional dyspnea and chronic sinusitis, radiologically by diffuse small nodules, and histologically by chronic inflammatory lesions around respiratory
bronchioles. The current DPB diagnostic criteria still refers to the guidelines proposed by a working group of the Ministry of Health and Welfare of Japan. The diagnostic criteria are: (i) persistent cough, sputum and exertional dyspnea; (ii) a history of, or current chronic sinusitis; (iii) bilateral diffuse small nodular shadows on a plain chest X-ray or centrilobular micronodules on chest CT. (iv) coarse crackles; (v) FEV1/FVC <70% and PaO2 <80 mmHg; and (vi) titer of cold haemagglutinin ≥64. Definite cases should fulfill criteria 1, 2 and 3, and at least two of criteria 4, 5 and 6.

Herein, we report two cases whose typical clinical manifestations and auxiliary examinations meet the above diagnostic criteria 1 to 5, but they are different in onset, clinical manifestations and disease progression. Below, we will summarize the similarities and differences of this two cases.

The case 1 (elder sister) had onset symptoms of chest tightness and wheezing. The dyspnea symptoms were earlier than those of cough and expectoration. Her sinusitis symptoms predate respiratory symptoms for about 8 years. Case 1 was characterized by recurrent respiratory tract infection in the early stage of the disease and infected with Pseudomonas aeruginosa and Mycobacterium tuberculosis infection in the late stage. The case 2 (younger sister) had onset symptoms of cough and hemoptysis. The symptoms of dyspnea were later than those of cough and expectoration. Her sinusitis symptoms were 5 years later than respiratory symptoms. Case 2 was characterized by paroxysmal wheezing. Before being admitted to our hospital, the case 2 received asthma medication for 8 years, but the symptom of paroxysmal wheezing were not well controlled.

There are many similarities in the clinical manifestations of the two cases. They all got sick from adolescence and suffered from chronic sinusitis for many years. They all had progressive aggravation of exertional dyspnea. Hypoxemia was found in the early stage of the disease, which was aggravated by repeated infections in the later stage. Before being diagnosed with DPB, case 1 had been misdiagnosed with chronic bronchitis for many years, while case 2 had been only diagnosed with bronchial asthma for many years. Because of misdiagnosis or missed diagnosis, they all missed the opportunity of early treatment, leading to further aggravation of their condition. They were all in the advanced stage of DPB at the time of diagnosis. They had diarrhea adverse reactions during azithromycin treatment and did not use macrolide antibiotics regularly for a long course.

They had similar clinical manifestations and were finally diagnosed as DPB despite living in different environments since childhood. Genetic factors may be the main influencing factors. We suspect that the disease susceptibility of the two sisters may be caused by their parents’ consanguineous marriage. At present, China lacks large-scale epidemiological data of DPB and its own diagnostic criteria, and the pathogenesis is still unclear. The influence of consanguineous marriage on this disease remains to be further studied.

DPB is often complicated with Pseudomonas aeruginosa, Haemophilus influenzae, Klebsiella pneumoniae and other infections. Pseudomonas aeruginosa is a pathogen that can provoke an intense inflammatory response leading to persistent airway inflammation and airway structural damage. It was more frequently detected in DPB patients with bronchiectasis, which was partly responsible for the poor therapeutic outcomes. The case 1 was infected with Pseudomonas aeruginosa in the advanced stage of the disease. The patient’s pulmonary function was worse than before. It was considered that the chronic colonization of Pseudomonas aeruginosa is associated with a greater decline in pulmonary function, and more frequent deterioration, hospitalization as well as increased mortality rate. In addition, pulmonary dysfunction may be a natural consequence of long-term chronic airway inflammation and recurrent infectious episodes. The case 2 was complicated with bronchiectasis, but no P. aeruginosa infection has yet occurred. Further follow-up is required for the occurrence of P. aeruginosa infection in the following course of disease.

Secondary tuberculosis infection in DPB patients is very rare. Case 1 developed tuberculosis infection after long-term corticosteroid use (12 months). We know that corticosteroid has anti-inflammatory and immunosuppressive effects in DPB treatment. Corticosteroid can quickly relieve the dyspnea symptoms and accelerate the absorption of chronic airway inflammation. It is mainly suitable for those who still have obvious dyspnea after treatment with macrolides, or patients with slow absorption of small pulmonary nodules. The treatment course of corticosteroids should be shorter than that of macrolides, which varies from person to person. However, long-term use of corticosteroids has a progressive destructive effect on human immune function,
reducing the autoimmune defense mechanism and increasing the risk of various infectious diseases, especially tuberculosis infection.\(^{10}\) Long-term use of corticosteroids is likely to induce tuberculosis or lead to the deterioration of the original tuberculosis. Therefore, we should guard against the occurrence of pulmonary tuberculosis for DPB patients who use corticosteroids for a long time. Case 1 is currently in the advanced stage of the disease and has just finished anti-tuberculosis treatment. The prognosis of this patient needs further follow-up.

DPB has a very well-established relationship with bronchiectasis. DPB can occur simultaneously with bronchiectasis or progress to bronchiectasis in its advanced stage. The coexistence of DPB and bronchiectasis has been assumed a more severe syndrome, which predicts a poor outcome of maintenance macrolide therapy and an increased exacerbation risk in DPB patients.\(^9\) In our case 2, the patient’s condition was repeated, persistent, and diarrhea adverse reaction occurred during azithromycin treatment. The poor prognosis may be associated with the coexistence of DPB and bronchiectasis. The cough, expectoration and chest imaging changes of the case 2 improved obviously after the treatment with DPB, but the paroxysmal wheezing symptom was not well controlled, and the symptom could be obviously relieved after using anti-spasmodic drug such as tiotropium bromide powder inhalant. And the patient had been diagnosed with bronchial asthma before the diagnosis of DPB. This is consistent with the diagnostic criteria of DPB combined with bronchial asthma (Table 3).

DPB and asthma are obstructive airway diseases, which are difficult to make a clear diagnosis when they co-exist. The cough, expectoration and chest imaging changes of the case 2 improved obviously after the treatment with DPB, but the paroxysmal wheezing symptom was not well controlled, and the symptom could be obviously relieved after using anti-spasmodic drug such as tiotropium bromide powder inhalant. And the patient had been diagnosed with bronchial asthma before the diagnosis of DPB. This is consistent with the diagnostic criteria of DPB combined with bronchial asthma (Table 3).

DPB is a complex pulmonary disease that can be associated with many diseases, such as myasthenia gravis with thymoma,\(^{11}\) rheumatoid arthritis,\(^{12,13}\) lung cancer,\(^{14}\) IgA nephropathy,\(^{15}\) asthma\(^{16–18}\) etc. To date, one case report of DPB complicated with asthma and bronchiectasis in a 48-year-old Irish woman on PubMed,\(^{19}\) and one case report of DPB complicated with tuberculosis in a 12-year-old Chinese child on CNKI\(^{20}\) have been published. The co-existence of DPB and pulmonary tuberculosis, and the co-existence of DPB with both asthma and bronchiectasis are rare. However, the co-existence of DPB with either asthma or bronchiectasis has been reported relatively frequently. Similarly, there are few reports of DPB family clustering.\(^{21–24}\)

In our report, the case 1 was complicated with tuberculosis and pseudomonas aeruginosa infection in the course of DPB, accompanied by respiratory failure. The case 2 suffered from DPB complicated with bronchial asthma and bronchiectasis. They were all in advanced stage of DPB and presented with poor therapeutic effects. The complexity of the disease contributed to their recurrent, persistent and difficult recovery. The two sisters was treated with azithromycin for 2 years but showed no signs of recovery. The duration of treatment remains unclear. Their prognosis needs further follow-up evaluation.

DPB is strongly associated with an HLA class I gene. Studies have shown that DPB is closely related to HLA-A11 and HLA-B54.\(^2\) However, the two sisters with DPB were both negative for HLA-A11 and HLA-B54, but positive for HLA-A24 and HLA-B13. Interestingly, their father and younger brother were positive for HLA-A11, but there was no evidence of diffuse panbronchiolitis. Besides, the case 2 (the younger sister) and the mother were both positive for HLA-A2. It was reported that HLA-A2 may be a genetic factor contributing to the relatively low incidence of DPB in Chinese population and may be involved in the process of presentation and recognition.\(^{25,26}\) However, there was no significant difference in the expression of HLA-A2 between DPB population and non-DPB population in Japan and South Korea. In our report, DPB patient was positive for HLA-A2, while non-DPB patients were positive for HLA-A11, which is different from previous literature reports. Further studies are needed to confirm the

### Table 3. Diagnostic criteria of DPB complicated with bronchial asthma.

1. Childhood onset
2. Family history of asthma
3. History of allergy or positive for allergens
4. On the basis of shortness of breath after activity, there is paroxysmal wheezing different from DPB
5. Cough, expectoration and imaging changes were obviously improved after DPB treatment, but the symptoms of paroxysmal wheezing were not well controlled, which could be obviously relieved by adding β2 receptor agonist.

Definite cases should fulfill criteria 4 and 5, and at least one of criteria 1, 2 and 3.
results and to identify the action of the HLA-A2 and HLA-A11 allele in DPB patients at the nucleotide sequence level. There are few reports about HLA-A24, HLA-B13, HLA-B40 and HLA-B46 in diffuse panbronchiolitis, and due to the small number of cases, its pathogenesis mechanism in DPB was not elaborated. Future research needs to be further clarified.

DPB was first detected and reported in Japan, and cases have been reported in South Korea, China, and other East Asian countries. Genetic predisposition to the disease has been assumed in Asians. To date, studies on DPB are mostly case reports, and the etiology and pathogenesis of DPB are still unclear. With the development of a series of molecular genes and immunological studies, it is generally considered that DPB is a disease involving a variety of factors, including genetic, immune abnormalities, environmental and infectious factors. Until the establishment of long-term macrolide therapy, the prognosis was generally poor. It is a treatable disease if detected early and treated correctly. Because it is responsive and reversible to long-term (at least 6 months) macrolide drug therapy, especially when administered early in the course. However, the clinical manifestations of DPB lack specificity, which is easy to be confused with chronic obstructive pulmonary disease, bronchial asthma, bronchiectasis, pulmonary tuberculosis and other chronic airway diseases. Most cases are misdiagnosed or missed and cannot be effectively treated for many years. It requires our clinicians to carefully assess the condition and make a differential diagnosis.

DPB is not rare in China, but under-diagnosis seems likely. Due to the lack of large sample study on DPB, its etiology, pathological mechanism and treatment criteria are not clear. Clinicians generally lack understanding of DPB and reports on this disease are not enough. Therefore, it is necessary for researchers and clinicians to make unremitting study in the future to clarify the etiology and pathogenesis of DPB and formulate a scientific and reasonable diagnosis and treatment standard.

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