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Diffuse panbronchiolitis in Thailand: Report of two cases and review of the literatures

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Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease of small airway of unknown etiology. It is characterized by chronic inflammatory reaction involving all layers of the respiratory and terminal bronchioles. We report two cases of DPB, diagnosed by surgical lung biopsies. Being more familiar with this entity, it would be possible to make an accurate diagnosis of DPB. Whenever questionable, surgical lung biopsy should be done to establish the diagnosis especially in Thailand where the prevalence of Tuberculosis is high. Once the correct diagnosis is made, the treatment is more promising. Long-term low dose of macrolides has been shown to be effective for the treatment of patient with DPB.

Keywords: *Diffuse panbronchiolitis, Small airway disease, Bronchiolectasis, Chronic obstructive lung disease, Lung.*

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เยาวเรศ วงศ์ศิวะวิลาส, เสาวณีย์ เย็นฤดี. โรคหลอดลมฝอยอักเสบในประเทศไทย: รายงานผู้ป่วย 2 รายและทบทวนวารสารการแพทย์. จุฬาลงกรณ์เวชสาร 2548 พ.ค; 49(5): 289 – 301

โรคหลอดลมฝอยอักเสบ (DPB) คือโรคอักเสบเรื้อรังของทางเดินหายใจขนาดเล็ก โดยไม่ทราบสาเหตุ โรคนี้มีการอักเสบเรื้อรังตลอดทุกชั้นของผนังหลอดลมฝอย เราได้รายงานผู้ป่วย DPB 2 ราย ซึ่งวินิจฉัยได้ด้วยการตรวจชันสูตรชิ้นเนื้อปอด การรู้จักคุ้นเคยกับโรคนี้ก็ทำให้สามารถให้การวินิจฉัยโรค DPB อย่างถูกต้องได้ เมื่อไรก็ตามที่การวินิจฉัยโรคยังไม่ได้ผลแน่นอน ก็ควรที่จะตัดชิ้นเนื้อปอดมาตรวจชันสูตรเพื่อให้ได้การวินิจฉัยที่ถูกต้อง โดยเฉพาะอย่างยิ่งในประเทศไทยที่มีอุบัติการณ์ของวัณโรคสูง เมื่อได้วินิจฉัยถูกต้องแล้วการรักษาจะได้ผลดี การใช้ macrolides ด้วยขนาดยาต่ำแต่ในระยะยาวให้ผลในการรักษาผู้ป่วยโรค DPB ได้เป็นอย่างดี

คำสำคัญ : *โรคหลอดลมฝอยอักเสบ,โรคหลอดลมฝอย, หลอดลมฝอยขยายตัว, โรคหลอดลมหายใจอุดกั้น, ปอด*

Diffuse panbronchiolitis (DPB) is a chronic inflammatory disease of small airways of unknown etiology. It is characterized by inflammatory process restricted largely to the respiratory and terminal bronchioles. Clinical features of DPB include chronic productive cough with mucopurulent sputum, dyspnea on exertion, and diffuse micronodular opacities in the background of hyperinflated lungs on chest radiography. Spirometry shows obstructive or mixed obstructive-restrictive patterns with marked abnormalities of gas exchange. [1-2]

DPB has been described in Japan since the early 1960's.[2-6] Although, it has been well recognized among Japanese and later among Chinese,[7-10] only sporadic cases have been reported in Koreans,[11, 12] Caucasians, [13, 14] African-Americans and Hispanics. [14,15] In Thailand, the first three cases of DPB were reported in 1999 by Chantarotorn et al. [16] The Thai profile included two Thai patients and one Chinese immigrant. The paucity of well documented cases of DPB in Thailand and other countries outside Japan could reflect a lack of awareness of this disease among chest physicians, radiologists, and pathologists. Alternatively, DPB may be truly uncommon outside Japan. Whatever it is, rapid and accurate diagnosis of DPB is of paramount importance. Unrecognized DPB carries serious consequences as this condition is highly responsive to treatment with long-term low dose of erythromycin or other macrolides but progressively worse or may be fatal if untreated.[17-20] We therefore report two histologically proved cases of DPB in Thai patients, diagnosed by surgical (open and video-assisted thoracoscopic) lung biopsies. We also did an extensive review of the literatures and addressed diagnostic points.

Case 1

A 65-year-old Thai married woman had had the history of productive cough with green sputum and dyspnea on exertion for 20 years. Her symptoms were progressively worse in the past 6 years. She was a farmer who denied drinking, smoking or any other medical illness. She had been treated as a case of chronic bronchitis and was later referred to this hospital. She admitted of having chest pain, fever, excessive sweating and a loss of appetite in the past month. Physical examination revealed rhonchi and crackles of lungs and no clubbing of the fingers. Chest X-rays showed diffuse fine nodular opacities of both lungs. She was given amoxicillin and liquid expectorant to take at home and was told to return for further investigation. A complete blood count revealed mild anemia. Chemistry profiles were within normal limits. Sputum examination for acid-fast bacilli was negative on three occasions. Hemophilus influenzae was isolated from sputum culture. Carcinoembryonic antigen (CEA) was 5.3 (normal 0-5 ng/ml). Her clinical data are shown, (Table 1). Pulmonary function test was consistent with a mixed obstructive and restrictive pattern, (Table 2). High-resolution computed tomographic (HRCT) scan was compatible with small airway disease, (Figure 1). She did not respond to the initial treatment with oral antibiotic and expectorant. An open lung biopsy at the right upper lobe demonstrated changes of DPB, (Figure 2-4). She was treated with 30 mg/day of prednisone for one month with no improvement. Upon her return, an additional one-month supply of roxithromycin and prednisone was given. She was thereafter lost to follow-up.

Table 1. Clinical findings of patients with diffuse panbronchiolitis.

Clinical Data	Case 1	Case 2
Age	65	60
Gender	Female	Male
Race	Thai	Thai
Occupation	Farmer	Farmer
Symptoms		
Chronic cough	Yes	Yes
Sputum	Green, Large amount	Green, 180 ml/day
Dyspnea	Yes	Yes
Chest pain	1 month	No
Fever	1 month	No
Weight loss	6 kgs in 1 years	No
Duration of illness	20 years	6 years
Co-existent with sinusitis	Not known	Maxillary sinusitis, bilateral
History of smoking	Never smoker	Never smoker
Physical Examination		
Rhonchi and crackles	Yes	Yes
Wheezing	No	Yes
Clubbing of the fingers	No	No
Mellioid titer	NA	Negative
Rheumatoid factor	NA	Negative
Mycoplasma titer	NA	Less than 1:40
Cold agglutinin	NA	Less than 1:32
Sputum Exam for AFB	Negative 3 times	Negative 3 times
Sputum Culture	*Hemophilus influenzae*	*Moraxella catarrhalis*
Electrocardiogram	Sinus Tachycardia, occasional PVC	Within normal limit

Abbreviations: NA = Not available
AFB = Acid-fast bacilli
PVC = Premature ventricular contraction.

Table 2. Pulmonary function test.

Pulmonary function test	Case1			Case 2					
	Before treatment			Before treatment			3 months after treatment		
	Pred	Best	% Pred	Pred	Best	% Pred	Pred	Best	% Pred
Spirometry									
FVC (Liters)	2.40	1.28	53%	3.36	1.91	57%	3.31	2.16	65%
FEV1 (Liters)	1.72	0.81	47%	2.53	1.01	40%	2.46	2.11	86%
FEV1 / FVC (%)	73	63		74	53		74	98	
PEF (Liters/Second)	5.00	1.16	23%	6.57	1.15	17%	6.50	5.98	92%
Lung Volumes									
VC (Liters)	2.40	1.28	53%	3.36	2.00	59%	3.31	2.26	68%
TLC (Liters)	3.86	3.60	93%	4.55	4.41	97%			
RV (Liters)	1.47	2.32	158%	1.70	2.41	141%			
RV / TLC (%)	39	64		36	55				
Diffusion									
DLCO (ml / Minute / mmHg)	11.30	7.70	68%	17.00	10.90	64%			
DLCO / VC (L / Minute / mmHg)	3.79	4.25	112	3.96	3.65	92			

Abbreviations: FVC = forced vital capacity

FEV1 = forced expiratory volume at 1 second

PEF = peak expiratory flow

VC = vital capacity;

TLC = total lung capacity

RV = residual volume

DLCO = diffusion limitation of carbon monoxide (measures diffusion capacity of the lung).

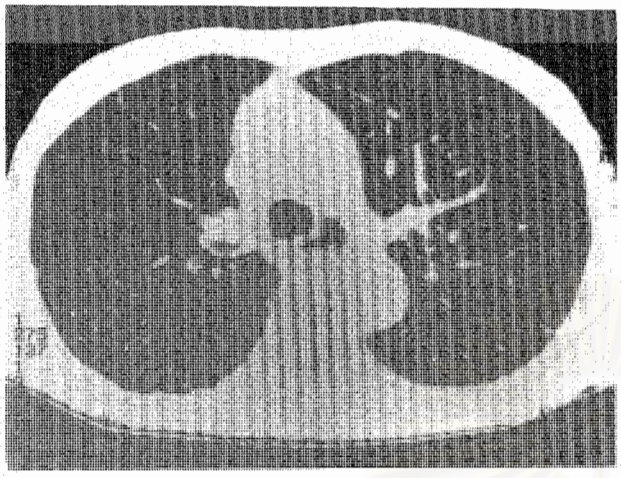

Figure 1. Inspiratory HRCT of case 1 shows numerous small round and branching linear opacities throughout both lungs, typical of the 'tree-in-bud' pattern of small airway disease. Slight dilatation of small bronchi is also seen.

Figure 2. Open lung biopsy of case 1 shows localization of chronic inflammation to the respiratory bronchiole (RB) and the adjacent tissue. Dilated RB containing acute inflammatory exudate is seen. RB is markedly dilated and its diameter is much larger than its companion pulmonary artery branch at its top, (H&E section X100).

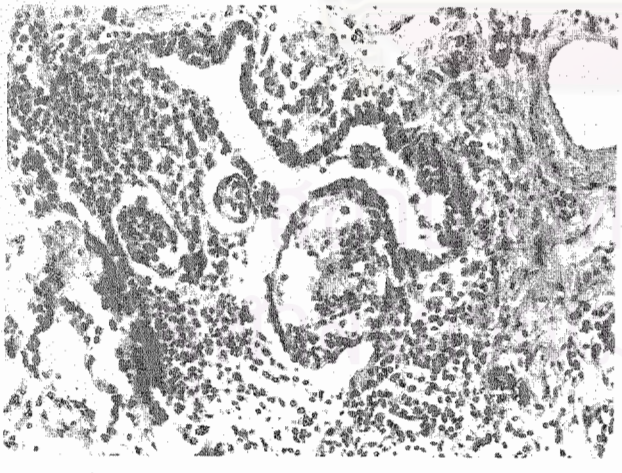

Figure 3. Open lung biopsy of case 1 shows peri-bronchiolar inflammation and dilated RB containing lots of neutrophils, macrophages, and mucus, (H&E section X 200).

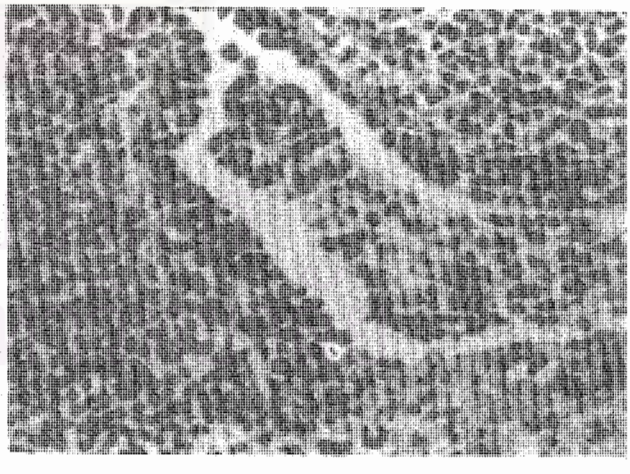

Figure 4. Open lung biopsy of case 1 shows dilated RB and peri-bronchiolar infiltrates with chiefly lymphocytes, mononuclear cells and some plasma cells. Neutrophils are present in the bronchiolar epithelium and bronchiolar lumen, (H&E section X 600).

Case 2

A 60-year-old Thai married man was referred to this hospital with the history of chronic productive cough with green sputum, exertional dyspnea, nose congestion, and post-nasal drainage for 6 years. His symptoms were progressively worse in the past year. He admitted of losing weight about 6 kilograms in one year. He was given ampicillin and bronchodilater with slight improvement. However, because of persistent dyspnea and productive cough, he was referred to this hospital. He was a farmer who denied drinking, smoking or any other medical illness. Physical examination revealed rhonchi and wheezing of lungs and no clubbing of the fingers. His complete blood count and chemistry profiles were within normal limits. Sputum examination for acid-fast bacilli was negative on three occasions. *Moraxella catarrhalis* was isolated from sputum culture. Rheumatoid factor was negative. Mycoplasma titer was less than 1:40 and cold agglutinin was less than 1:32. His clinical data are shown, (Table 1). Pulmonary function test was compatible with a mixed obstructive and restrictive pattern, (Table 2). Chest X-rays revealed diffuse micronodular infiltrates of both lungs in the background of hyperinflated lungs. Sinus X-rays showed bilateral maxillary sinusitis. HRCT scan is shown, (Figure 5). A video-assisted thoracoscopic (VAT) lung biopsy at the right lower lobe demonstrated changes of DPB, (Figure 6). He was treated with low dose erythromycin for three months with miraculous improvement. His productive cough and dyspnea improved after one month of treatment. After 3 months of treatment, he no longer had dyspnea or cough and a repeat lung function test demonstrated marked improvement, (Table 2). A repeat chest radiograph showed completely clear up of the lung infiltrates. Further follow-up is not available.

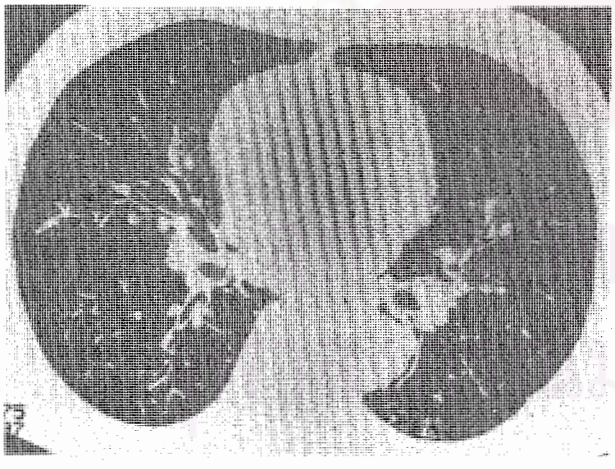

Figure 5. Expiratory HRCT of lower lung of case 2 shows diffuse centrilobular nodules and branching linear opacities throughout both lungs, typical of the 'tree-in-bud' pattern of small airway disease. Dilatation and thickening of small bronchi and bronchioles are observed. This expiratory film also shows multiple areas of air trapping.

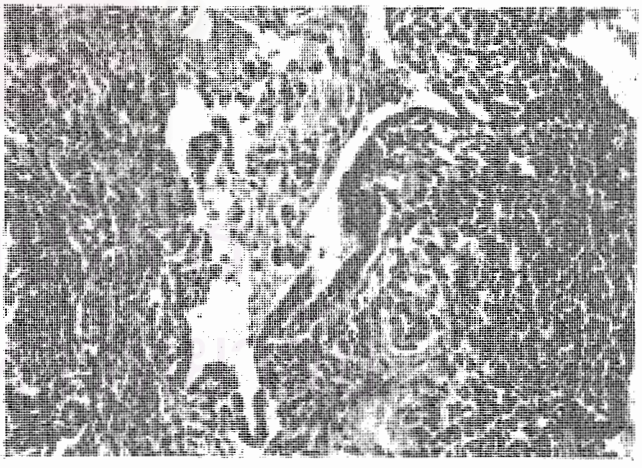

Figure 6. VAT lung biopsy of case 2 shows a markedly dilated RB containing neutrophils, macrophages, and mucus, and chronic inflammation involving the entire bronchiolar wall. A partial destruction of bronchiolar epithelium is noted, (H&E section X 400).

Discussion

The name 'diffuse panbronchilitis' (DPB) was first proposed as a new distinct entity in Japan in 1969. Diffuse refers to the distribution of the lesion throughout both lungs and pan refers to spreading of inflammatory reaction to all layers of the respiratory bronchioles and the surrounding tissue. As macrolides treatment is effective for DPB, familiarity with its clinical and pathologic features is urgently needed.

Homma et al reported a collection of more than 1,000 probable cases of DPB after a nation-wide survey of Japan in 1983.[2] They found 82 histologically confirmed cases in their surveys from 1978 through 1980. DPB appears to be almost restricted to the Japanese and less common among other Asians. It is also rare in North America and Europe. An increase Bw54 or Bw54-related haplotype was seen among patients with DPB and juvenile onset diabetes mellitus.[21] The association of DPB with chronic sinusitis was found in 75 % to 78 % of cases.[2, 10] Other diseases seen in association with DPB included ulcerative colitis,[22] Churg-Strauss syndrome,[23] Sjogren's syndrome, [24] adult T-cell leukemia, [25] and non-Hodgkin's lymphoma.[26]

Bronchiolitis in infants is common worldwide and well recognized. However, chronic respiratory bronchiolitis in adults has not been thoroughly familiar with. In 1971, Macklem et al reported seven cases of small airway diseases under the generic name of chronic obstructive disease of small airways. [27] Two years later, Gosink et al reported idiopathic cases of obstructive airway disease under the name 'idiopathic bronchiolitis obliterans. [28] In 1983, Homma et al commented that four of the seven cases reported by Macklem et al and two reported cases by Gosink et al were most likely the examples of DPB as defined in their publication.[2] In 1994, Iwata et al reported seven cases of DPB and twenty examples of DPB-like lesion found in a large review of cases with diffuse lung disease.[29] In their report, three out of seven cases were definite DPB cases both clinically and pathologically. The remaining four cases showed typical histopathologic features of DPB but lacked several clinical criteria.

The diagnosis of DPB is not always easy to establish. The clinical diagnostic criteria for DPB as proposed by Homma et al in 1983 have been very helpful.[2] DPB has been accepted as a clinicopathologic entity with the following clinical diagnostic criteria [2]: 1. symptoms of chronic productive cough and exertional dyspnea; 2. Physical signs of rales and rhonchi; 3. a chest radiograph showing diffusely disseminated fine nodular shadows, chiefly in the lower lung fields with hyperinflation of the lungs; and 4. Pulmonary function studies showing at least three of the four listed abnormalities: forced expiratory volume in one second less than 70 %, vital capacity less than 80 % of the predicted value, residual volume greater than 150 % of the predicted value, or PaO2 less than 80 mmHg.

HRCT scan of the chest can demonstrate the location of pathologic changes within a lobule and may be helpful in the differential diagnosis of diffuse lung diseases, thus a valuable diagnostic tool for DPB. [30-33] Xie et al reported that based on clinical diagnostic criteria, DPB was clinically considered prior to histopathologic diagnosis in only 22 % of patients with the remaining 78 % of cases missed or mistaken for other diseases.[10] Apparently, clinical and radiological features of DPB overlap among other

group of chronic obstructive conditions of lungs, such as chronic bronchitis, bronchial asthma, emphysema, bronchiectasis, and bronchiolitis obliterans.

It has become increasingly recognized that some cases of DPB diagnosed solely on clinical findings are in fact examples of bronchiectasis and chronic cellular bronchiolitis, and on the other hand, some cases that do not fulfil the clinical diagnostic criteria of DPB show typical pathologic features of DPB.[29] The question is what would be the gold standard for the diagnosis of DPB. We must be well aware to the fact that DPB was first defined on histopathologic basis and clinical diagnostic criteria later developed from the study of those histologically confirmed cases.[2] In addition, histopathologic features of DPB are quite distinct. Therefore, histopathologic confirmation of the diagnosis is of fundamentally importance. Unfortunately, surgical (open or VAT) lung biopsy is not always practical for all cases.

Transbronchial lung biopsy (TBLB) may be an alternative approach to obtaining specimen for the diagnosis. The problem is TBLB specimens are generally not large enough to allow an adequate observation of small airway disease and reach a definitive diagnosis of DPB. It oftentimes discloses a non-specific inflammation. In fact, eight of nine reported cases by Xie et al had TBLB done before surgical lung biopsies and showed non-specific inflammation. [10] Randhawa et al reported three cases of DPB diagnosed by open lung biopsies.[34] Their report indicated that two of the three patients had non-diagnostic TBLB but subsequent open lung biopsy showed DPB. TBLB is useful in excluding infection, whereas surgical lung biopsy demonstrates more detail of pathology patterns associated with DPB. We agree with most authors' recommendation that in difficult cases, the diagnosis of DPB should be based on clinicopathological features and the exclusion of other diseases.[10, 29, 34]

We would like to emphasize that the pathologist's approach to diagnosing a diffuse lung disease requires the integration of clinical and radiological information with histopathologic findings. HRCT images generally reflect gross morphologic features and equate to the gross examination of the lung by the pathologist. In case of atypical clinical manifestations, the diagnosis of DPB must rely on histopathologic features.

We have presented two cases of DPB which was considered clinically to represent diffuse interstitial lung disease. Although, clinical diagnosis of our reported cases was not made prior to the surgical lung biopsies, they were considered definite cases of DPB after a retrospective review of clinical and radiological data. Summary of diagnoses according to clinical, radiological and pathological features are shown, (Table 3). Diagnosing lung diseases in Thai patients is one of the most difficult tasks that physicians have encountered as it is well known that Tuberculosis is the great imitator and its prevalence is high in Thailand.

The surgical lung biopsies of our reported cases demonstrated thickening of bronchiolar wall with infiltration of chiefly lymphocytes, some plasma cells, and mononuclear cells, and extension of the inflammatory process into peribronchiolar area, the adjacent alveoli and interstitium. The inflammatory process restricted in its distribution to the respiratory and terminal bronchioles.

Table 3. Summary of diagnoses according to clinical, radiological and pathological features.

Diagnosis	Case 1	Case 2
Clinical	Diffuse interstitial lung disease Chronic bronchitis	Diffuse interstitial lung disease Emphysema Miliary Tuberculosis Idiopathic interstitial fibrosis
Radiological		
Chest X-rays	Diffuse fine nodular opacities in the background of hyperinflated lungs.	Same
HRCT of the chest	Bronchiolitis obliterans Diffuse panbronchiolitis	Pulmonary Tuberculosis Viral pneumonia Hypersensitivity pneumonitis Diffuse panbronchiolitis
Pathological	Diffuse panbronchiolitis Other diseases such as Tuberculosis, Bronchiolitis obliterans, Bronchiectasis, Extrinsic allergic alveolitis are excluded.	Same

Other prominent features of our reported cases included bronchiolectasis of the respiratory bronchioles and the terminal bronchioles, intraluminal plugging of mucus and neutrophils, and infiltration of neutrophils in the bronchiolar epithelium. There were no eosinophils or microgranulomas to suggest extrinsic allergic alveolitis. The cases did not fit into the spectrum of bronchiolitis obliterans because there were no plugs of organized connective tissue and inflammatory cells in the bronchiolar lumen that obliterated the terminal airways. Finally, there was no granuloma seen in the biopsy specimens.

Same as some other reports,[10, 29] we did not see foamy macrophages in case 1 and found only few of them in case 2. Although, the accumulation of foamy macrophages is a distinct feature of DPB, it is not specific for this condition since similar changes can occur in association with other diseases such as cystic fibrosis and bronchiectasis. Occasional foci of interstitial foam cells associated with acute inflammation and intraluminal granulation tissue were reported in the cases of Wegener's granulomatosis, bronchocentric granulomatosis, and Hodgkin's disease.[29] A helpful diagnostic clue to DPB is seen by low-power microscopy which shows fine nodules of inflammatory infiltrates around the respiratory and terminal bronchioles and normal or hyper-distended alveoli in the intervening lung parenchyma.

The findings of bronchiolectasis and bronchiolar plugging of mucus and neutrophils in DPB have been well recognized but the presence of neutrophilic infiltration in the bronchiolar epithelium has not previously been described. Perhaps, it has been overlooked or considered a trivia. We believe this

finding is significant and it is consistent with the most recent report of Kim, et al who examined the relationship between epidermal growth factor receptor (EGFR) expression in the bronchiolar epithelium with neutrophilic inflammation and mucus hypersecretion in the tissue of DPB patients.[35] They suggested that mucus hypersecretion was due to goblet cell metaplasia and degranulation of goblet cells that were closely associated with bronchiolar neutrophilic inflammation and EGFR expression. Although, bronchiolar neutrophilic inflammation is probably not the original cause of DPB, it most likely plays an importance role in the pathogenesis of DPB. More research is needed and hopefully will shed some light onto the genuine etiology of this condition.

Being more familiar with this entity, it would be possible to make an accurate diagnosis of DPB. Whenever questionable, surgical lung biopsy should be done to establish the diagnosis especially in Thailand where the prevalence of Tuberculosis is high. Once the correct diagnosis is made, the treatment is more promising.

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