Bronchiolitis in Kartagener's syndrome

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ABSTRACT: The association of diffuse bronchiolitis in patients with Kartagener's syndrome (KS) has not been reported previously. The aim of this study was to present the morphological characteristics of bronchiolitis in patients with KS.

Eight patients (four males, four females; mean age 37.9±18.7 yrs), clinically diagnosed as KS with the classical triad of chronic pansinusitis, bronchiectasis and situs in*versus* with dextrocardia, were evaluated.

Routine chest radiography showed bronchiectasis and dextrocardia in all patients. Chest computed tomography (CT) showed diffuse centrilobular small nodules up to 2 mm in diameter throughout both lungs in six out of eight patients. Pulmonary function tests revealed marked obstructive impairment in all patients (forced expiratory volume in one second 57.0±11.3%, residual volume/total lung capacity 45.0±12.7%, maximum midexpiratory flow 0.92±0.72 L·s^{-1}, forced vital capacity 74.1±12.2% (all mean±SD)). The examination of cilial movement of the bronchus revealed immotility in all of the five patients examined. The ultrastructure showed ciliary dynein arm defects in all patients. Histopathological examination of lung specimens obtained at autopsy or by video-assisted thoracoscopic surgery showed obliterative thickening of the walls of the membranous bronchioli with infiltration of lymphocytes, plasma cells and neutrophils, but most of the distal respiratory bronchioli were spared and alveolar spaces were overinflated. Pathologically, the diffuse centrilobular small nodules on the chest CT mainly corresponded to membranous bronchiolitis.

This is the first report demonstrating that the association of diffuse bronchiolitis might be one of the characteristic features of the lung in Kartagener's syndrome.
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Although Kartagener's syndrome (KS) characterized by the triad of chronic pansinusitis, bronchiectasis and situs in*versus* with dextrocardia [1] is well known, the association of diffuse bronchiolitis has not been previously recognized in patients with this syndrome. KS is also known as immotile-cilia syndrome [2, 3] or as a primary ciliary dyskinesia (PCD) [4, 5]. On the other hand, in diffuse panbronchiolitis (DPB) the lesions are principally located in the respiratory bronchioli and cases have been reported mainly in Japanese adults [6]. Recently in Japan, PCD has been discussed as a possible aetiological factor in DPB [7]. Therefore, there might be a considerable histopathological overlap in bronchiolitis between KS and DPB. The aim of this study was to present the morphological characteristics of bronchiolitis in patients with KS. In addition, the morphological differences of bronchiolitis between KS and DPB are discussed.

Subjects and methods

Eight patients (four males and four females, mean age 37.9±18.7 yrs), clinically diagnosed as KS with the classical triad during the period 1986–1996, were evaluated.

Clinical features

Clinical symptoms, the properties of the sputum and treatment were evaluated.

Radiography

Chest radiographs and chest computed tomography (CT) images were evaluated before treatment.

Pulmonary function tests

The total lung capacity (TLC), forced expiratory volume in one second (FEV1), maximal midexpiratory flow (MMF), delta N_2, carbon monoxide diffusing capacity of the lung and arterial blood gases were measured according to standard methods with a Chestac-55V (Chest Co., Ltd., Tokyo, Japan) and an ABL510 (Radiometer Co., Ltd., Copenhagen, Denmark).

Morphological analysis

Mucociliary function. In five out of eight patients, ciliary beat frequency (CBF) was evaluated. Samples of ciliated bronchial epithelium were suspended in a nutrient medium (Medium 199; Flow Laboratories, Irvine, Scotland). CBF was measured photometrically in at least 10 different areas of each sample while the temperature was maintained at 37°C with a warm stage as described in a previous report [8].

Ultrastructure. In all eight patients, ciliary ultrastructure was evaluated. The bronchial epithelium was immediately fixed in cacodylate-buffered 2.5% glutaraldehyde,

Table 1. – Clinical features of the study patients with Kartagener's syndrome

Patient	Age yrs	Sex	SI	Respiratory symptom (onset age yrs)	Chronic pansinusitis	Otitis media	Infertility (married)	Situs inversus	Sputum production g·day^{-1}	Sputum culture	Treatment
1	35	F	0	Cough, sputum (9)	+	-	+ (Y)	+	100	*P. aeruginosa* *H. influenzae*	OFLX, EM, CAM
2	41	M	0	Cough, sputum (30)	+	-	+ (Y)	+	70	*P. aeruginosa*	OFLX, EM
3	50	F	0	Cough, sputum (12)	+	+	- (Y)	+	80	*P. aeruginosa*	OFLX, EM
4	72	M	0	Cough, sputum (62)	+	+	- (Y)	+	30	*P. aeruginosa* *H. influenzae*	LVFX, CAM
5	21	F	100	Cough, sputum (18)	+	+	? (N)	+	72	*P. aeruginosa* *H. influenzae*	LVFX, EM
6	20	M	20	Cough, sputum (12)	+	+	? (N)	+	10	*H. influenzae*	EM
7	17	M	0	Cough, sputum (2)	+	+	? (N)	+	130	*P. aeruginosa*	LVFX, EM
8	47	F	0	Cough, sputum (46)	+	-	? (N)	+	48	*P. aeruginosa* *H. influenzae*	LVFX, EM

F: female; M: male; SI: Brinckman smoking index; DOE: dyspnoea on exertion; *P. aeruginosa*: *Pseudomonas aeruginosa*; *H. influenzae*: *Hemophilus influenzae*; OFLX: ofloxacin; EM: erythromycin; LVFX: levofloxacin; CAM: clarithromycin; +: with complication; -: without complication; (Y): yes; (N): no; ?: unknown.

post-fixed in osmium tetroxide, and processed for transmission electron microscopy. Transversely sectioned cilia were assessed at magnifications of $25,000 \times -100,000 \times$ with an H-600A electron microscope (Hitachi Co., Ltd., Tokyo, Japan) as described in a previous report [9].

Histopathology. Out of the eight patients, one underwent *post mortem* examination and two underwent video-assisted thoracoscopic surgery (VATS) as a diagnostic procedure. The lung specimens were fixed with 10% formaldehyde and embedded in paraffin from which 3 μm thick sections were cut and stained with haematoxylin-eosin and elastica van Gieson. The sections were mounted in aqueous mounting medium and observed by light microscopy to determine the characteristics of the bronchiolitis.

Results

Clinical findings

The clinical features of the eight patients with KS are shown in table 1. Respiratory symptoms, including a history of productive cough and exertional dyspnoea, were noted in all patients. The age at onset of respiratory symptoms was 2–62 yrs. There was a history of chronic pansinusitis in all patients, otitis media in five out of eight patients, infertility in two out of four married patients and situs inversus in all patients. The mean sputum production was 68 g·day^{-1}. Physical signs of wheezing and/or coarse crackles were audible upon aesculation of the chest in all patients. Examination of sputum revealed *Haemophilus influenzae* and/or *Pseudomonas aeruginosa* superinfection in all patients. Quinolone (ofloxacin or levofloxacin) and macrolide (erythromycin or clarithromycin) were effective for treatment of superinfection in most of the patients. One patient (3) died of progressive respiratory failure 38 yrs after the onset of respiratory symptoms.

Radiography images

Conventional chest radiographs showed dextrocardia and bronchiectasis in all patients. Chest CT showed diffuse centrilobular small nodules up to 2 mm in diameter throughout both lungs in six out of eight patients. Bronchiectasis and centrilobular small nodules were localized to the middle, the lingula and lower lobes in all patients. Hyperinflation was noted in four out of eight patients, tramlines in six out of eight patients, and atelectasis of the left middle lobe and pneumonia in two out of eight patients (table 2).

Table 2. – Chest radiography findings

Patient	Dextrocardia	Bronchiectasis	Centrilobular small nodules	Hyperinflation	Tramlines	Others
1	+	LML, LLL, RLing, RLL	-	+	+	Pneumonia
2	+	LML, RLL	-	-	+	
3	+	LML, LLL, RLing, RLL	+ (LLL, RLL)	+	-	Bullae
4	+	LML, LLL, RLL	+ (LLL, RLL)	-	-	
5	+	LML, LLL, RLing	+ (LLL, RLL)	-	+	Atelectasis of LML
6	+	LML	+ (LLL, RLL)	-	+	Atelectasis of LML
7	+	LLL, RLing, RLL	+ (LML, LLL, RLing, RLL)	+	+	
8	+	LML, LLL, RLing, RLL	+ (LLL, RLL)	+	+	Pneumonia

LML: left middle lobe; LLL: left lower lobe; RLing: right lingula; RLL: right lower lobe.

Table 3. – Pulmonary function tests

Patient	FVC L %	FEV1 L	FEV1/FVC %	RV/TLC %	ΔN2 %	MMF L·s⁻¹	DL,CO mL·min⁻¹· mmHg⁻¹ %	Pa,O2 mmHg	Pa,CO2 mmHg
1	2.09 (76)	1.27	61	44	16.3	0.78	ND	77	41
2	3.33 (84)	2.16	65	48	2.5	1.1	31.2 (139)	81	37
3	1.47 (56)	0.71	48	64	8.4	0.27	14.0 (81)	71	37
4	2.08 (66)	1.09	52	59	3.5	0.48	ND	71	46
5	2.81 (87)	1.69	60	33	3.5	1	23.2 (118)	84	37
6	4.36 (90)	3.25	74	29	1.9	2.53	37.7 (127)	80	42
7	2.78 (63)	1.03	37	33	18.5	0.29	28.4 (100)	86	37
8	1.79 (71)	1.06	59	50	1.5	0.93	17.3 (118)	75	45
Mean±SD	2.59±0.94 (74.1±12.2)	1.53±0.83	57.0±11.3	45.0±12.7	7.0±6.8	0.92±0.72	25.3±8.9 (113.8±20.5)	78.1±5.6	40.3±3.8

FVC: forced vital capacity; FEV1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; MMF: mean midexpiratory flow; DL,CO: carbon monoxide diffusing capacity of the lung; Pa,O2: arterial oxygen tension; Pa,CO2: arterial carbon dioxide tension; ND: not determined. (1 mmHg=0.133 kPa.)

Pulmonary function tests

Pulmonary function tests at the first visit revealed marked obstructive impairment, slight restrictive impairment and hypoxaemia in all patients (table 3).

Pathological findings

The examination of cilial movement of the bronchial epithelium revealed immotility in all five patients examined. The ultrastructure showed ciliary abnormalities, such as the absence of dynein arms, in all eight patients. These findings were consistent with previous reports of ciliary abnormalities associated with PCD [10].

Histopathological examination of the lung specimens obtained by autopsy or VATS showed inflammatory thickening of the walls of membranous bronchioli with infiltration of lymphocytes, plasma cells and neutrophils, while the distal respiratory bronchioli were slightly affected and alveolar spaces were overinflated, with destruction. In addition to these findings, obliterative bronchiolitis (OB), which showed obliteration of the membranous bronchioli by granulation tissue with inflammatory cell infiltration and/or lymphoid hyperplasia, was observed simultaneously in the same lung in patients 7 and 8 (table 4).

Pathologically, the diffuse centrilobular small nodules on the chest CT corresponded to the bronchiolitis, principally affecting the membranous bronchioli.

Case reports

Characteristic pathological features in two patients with KS are described.

Patient 7. A 17-yr-old male presented because of dyspnoea on exertion (DOE), cough and sputum. He had been suffering from productive cough since the age of 2 yrs. He had a history of chronic pansinusitis and otitis media. Lung auscultation revealed coarse crackles on the bilateral lower lung fields. Pulmonary function tests revealed obstructive impairment (FEV1 1.03 L, FEV1 (FEV1/forced vital capacity (L) × 100) 37%, MMF 0.29 L·s⁻¹). Sputum culture isolated *P. aeruginosa* Ciliary morphology of the bronchial epithelium revealed immotile cilia and defects of the dynein arms (fig. 1). Chest radiography showed dextrocardia, reticular shadows associated with tramlines and scattered fine nodular densities in both lung fields (fig. 2). Chest CT images showed dextrocardia, bronchiectasis and diffuse centrilobular small nodules throughout both lungs (fig. 3). The patient underwent VATS as a diagnostic procedure. Microscopy at low magnification of the lung specimen showed bronchiolitis in the centrilobular lesion associated with proximal bronchiolectasis and overinflation with focal emphysema of the alveolar spaces (fig. 4a). Higher magnification revealed that the walls of membranous bronchioli were thickened by fibrosis and infiltration of lymphocytes and plasma cells associated with or without peribronchiolar

Table 4. – Pathological findings

Patient	Lesions of bronchiolitis			Histopathological features					Pathological diagnosis	Sampling method (segment of lobe)
	RB	MB	Infiltrating cell	Bronchiolectasis	Pneumonia	LH	OB	Emphysema		
3	+	++	N, L, P	++	++	-	-	+ (Bullae)	Membranous bronchiolitis Respiratory bronchiolitis	Autopsy
7	+	+++	N, L, P	++	-	+	+	+ (FE, CE)	Membranous bronchiolitis OB	VATS (Rt. S8, S9)
8	+	+++	N, L, P, F	+	-	++	+	+ (FE)	Membranous bronchioloitis OB Respiratory bronchiolitis	VATS (Lt. S6, S8)

The intensity of the histopathological features is graded on a semiquantitative scale of - (none) to +++ (intense). RB: respiratory bronchiole; MB: membranous bronchiole; N: neutrophil; L: lymphocyte; P: plasma cell; F: foamy macrophage; LH: lymphoid hyperplasia; OB: obliterative bronchiolitis; FE: focal emphysema; CE: centrilobular emphysema; VATS: video-assisted thorascopic surgery; Rt. S8: anterior basal segment of the right lower lobe; Rt. 59: lateral basal segment of the right lower lobe; Lt. 56: superior segment of the left lower lobe; Lt. 58: anteromedial basal segment of the left lower lobe.

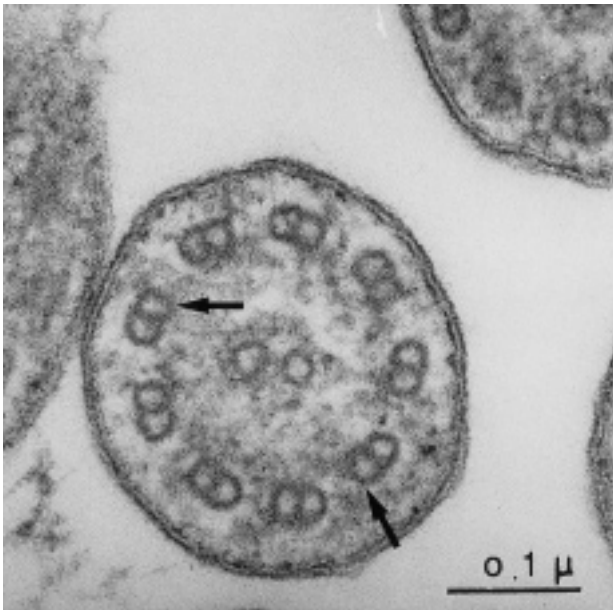Fig. 1. – Cross-section of a cilium shows the absence of inner and outer dynein arms (arrows) (patient 7; internal scale bar=0.1 µm).

lymphoid hyperplasia (fig. 4b). Some of these bronchioli showed OB where the lumina of membranous bronchioli were obliterated by fibrous scars (figs. 5a and b).

The schematic reconstruction of the sections focusing on the centrilobular lesions showed membranous bronchiolitis associated with peribronchiolar fibrosis, fibro-hyalinous scars, lymphoid hyperplasia and infiltration of neutrophils, lymphocytes and plasma cells. The alveolar spaces, alveolar ducts (AD) and respiratory bronchioli (RB) were dilated in association with focal emphysema (fig. 6). According to these pathological findings, this case was diagnosed as having membranous bronchiolitis, OB and peribronchiolar lymphoid hyperplasia with focal emphysema associated with KS.
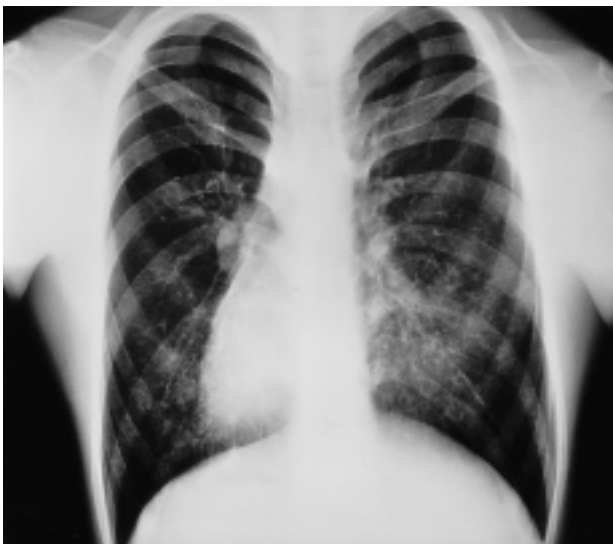
Fig. 2. – Chest radiograph showing dextrocardia, reticular shadows associated with tramlines and scattered fine nodular densities in both lung fields (patient 7).
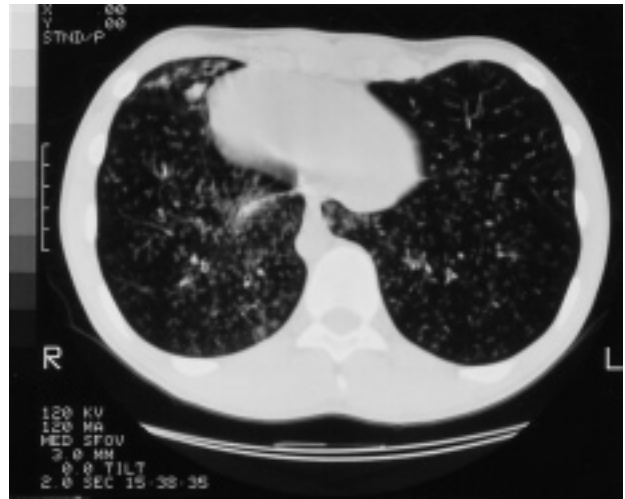

Fig. 3. – Chest computed tomography scan showing dextrocardia, bronchiolectasis and diffuse centrilobular small nodules throughout both lungs (patient 7).

Patient 8. A 47-yr-old female presented with a 1 yr history of cough and sputum. She had a history of chronic pansinusitis. Lung auscultation revealed coarse crackles on the bilateral lower lung fields. Pulmonary function tests revealed obstructive impairment with slight hypoxaemia (FEV1 1.06 L, FEV1 59%, MMF 0.93 L·s^{-1}, arterial oxygen tension 10 kPa (75 mmHg)). Sputum culture isolated *H. influenzae* and *P. aeruginosa*. Morphological analysis of the bronchial epithelium revealed immotile cilia and defects of the ciliary dynein arms. Chest radiography showed dextrocardia, reticular shadows associated with tramlines, bronchiectasis and scattered fine nodular densities in both lung fields. Chest CT images showed dextrocardia, bronchiectasis and diffuse centrilobular small nodules throughout both lungs (fig. 7). The patient underwent VATS for evaluation of histopathological features of these diffuse centrilobular lesions. Microscopy at a low magnification of the lung showed bronchiolitis in the centrilobular lesion and overinflated alveolar spaces with focal emphysema. Higher magnification revealed that the walls of membranous bronchioli were thickened by infiltration of lymphocytes and plasma cells accompanied by intraluminal inflammation (fig. 8a). Several lumina of the membranous bronchioli were obliterated by infiltration of neutrophils and mucus or desquamative epithelium associated with peribronchiolar lymphoid hyperplasia and fibrosis. The wall of a respiratory bronchiole was thickened by infiltration of lymphocytes and plasma cells accompanied by an accumulation of foamy macrophages (fig. 8b).

The schematic reconstruction of the sections focusing on the centrilobular lesions showed that membranous and respiratory bronchiolitis were associated with peribronchiolar fibrosis, lymphoid hyperplasia and infiltration of neutrophils, lymphocytes, plasma cells and foamy macrophages. The alveolar spaces, AD and RB were dilated. In the lumina of membranous bronchioli, granulation tissue and mucus were noted (fig. 9). According to these pathological findings, this case was diagnosed as having membranous bronchiolitis, OB and respiratory bronchiolitis with focal emphysema associated with KS.
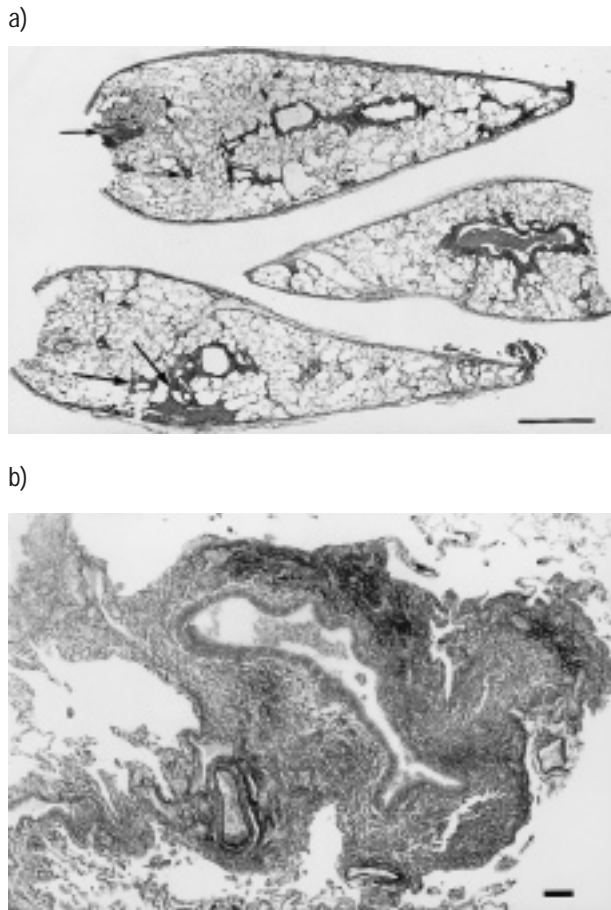
a)

b)

Fig. 4. – a) Low magnified microscopic appearance of the lung shows bronchiolitis (arrows) in the centrilobular lesion associated with proximal bronchiolectasis. The alveolar spaces are overinflated with focal emphysema (patient 7, elastica van Gieson stain; internal scale bar=3 mm). b) Wall of a membranous bronchiole is thickened by infiltration of lymphocytes and plasma cells accompanied by intraluminal inflammation (patient 7, elastica van Gieson stain; internal scale bar=73 µm).
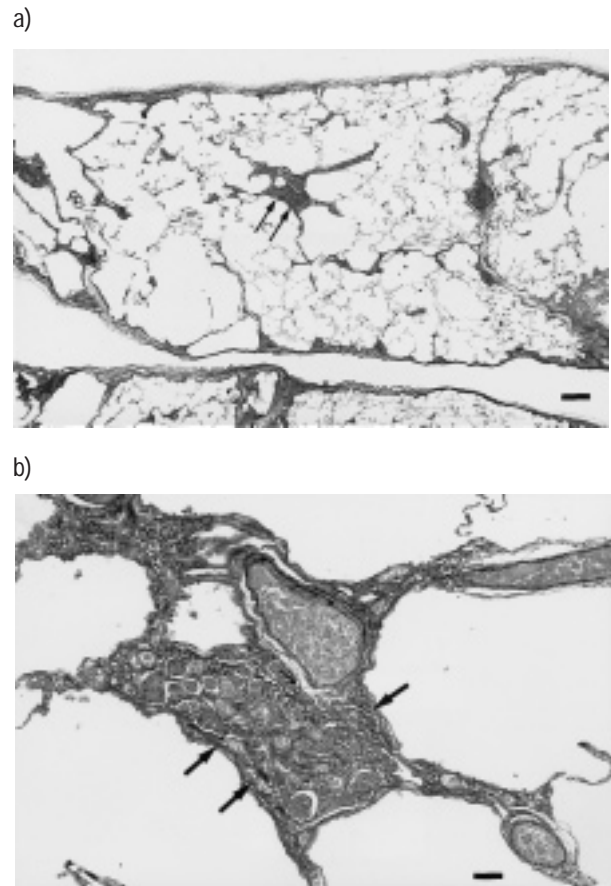
a)

b)

Fig. 5. – a) Low magnified microscopic appearance of the lung shows bronchiolitis (arrows) in the centrilobular lesion. The alveolar spaces are overinflated with focal emphysema (patient 7, elastica van Gieson stain; internal scale bar=360 µm). b) Lumen of a membranous bronchiole (arrows) is obliterated by a fibrous scar (patient 7, elastica van Gieson stain; internal scale bar=57 µm).

Discussion

In 1933, KARTAGENER [1] described a syndrome characterized by the triad of *situs in versus*, bronchiectasis and chronic pansinusitis. The disorder is inherited as an autosomal recessive trait. Males and females are affected equally. Recently, the syndrome has been classified as a PCD. Diagnosis of PCD is dependent on the demonstration of abnormal ciliary motility and ultrastructural defects of the cilia [4, 5]. In 1990, AMITANI *et al.* [7] reported nine cases of PCD, including six cases of KS, two cases of DPB and one case of bronchiectasis. They described diffuse micronodular shadows on the chest radiograph in one out of six patients with KS and in both patients with DPB. However, their report lacked histopathological analysis of diffuse micronodular lesions in these cases.

DPB has been noted in Japan since 1969 as a new clinicopathologic entity, characterized by respiratory bronchiolitis and peribronchiolitis which are diffusely disseminated throughout the lungs bilaterally, especially in the lower lobes, and diffuse centrilobular small nodules on chest CT [6, 11]. Furthermore, secondary bronchiolectasis in the middle lobe and/or lingula is frequently observed in pro-

gressive DPB [12]. Although the aetiology of DPB is as yet unknown, AMITANI *et al.* [7] also suggested that one of the aetiological factors of DPB might be PCD.

To the authors′ knowledge, this is the first report which describes the histopathological characteristics of the diffuse centrilobular nodules in patients with KS. In addition, a histopathological differences between KS and DPB was demonstrated.

In this study, six out of eight patients with KS showed diffuse centrilobular small nodules up to 2 mm in diameter throughout both lungs in addition to bronchiectasis and dextrocardia on chest CT. The lung tissue specimens in three out of these eight patients with KS provided evidence that the centrilobular small nodules on chest CT corresponded to the bronchiolitis mainly affecting the membranous bronchioli associated with infiltration of lymphocytes, plasma cells and neutrophils, but most of the distal respiratory bronchioli were spared and alveolar spaces were overinflated in association with focal emphysema or bullae. Additionally, two different histopathological patterns, one of constrictive OB and the another of respiratory bronchiolitis, were observed in the same lung. Small nodules and hyperinflation may be seen on the chest CT in constrictive OB [13–15]. According to these current findings, this study suggests that the histopathological features of the airway involvement in
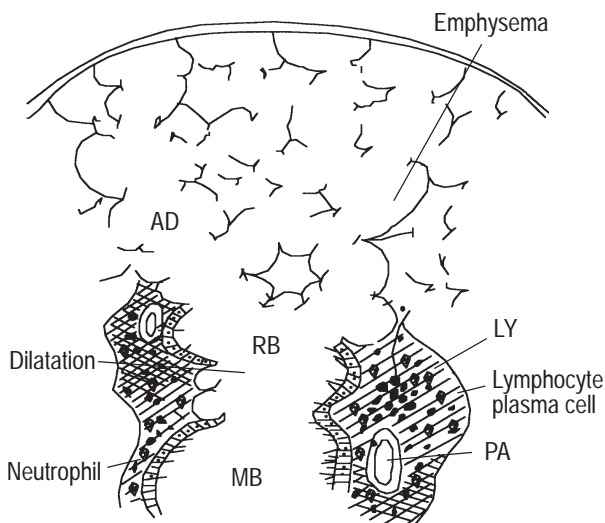
Fig. 6. – Schematic reconstruction of the sections focused on the centrilobular lesions of patient 7 showing the respiratory and membranous bronchiolitis associated with peribronchiolar fibrosis (▨), fibrohyalinous scar (■), lymphoid hyperplasia (LY) and infiltration of neutrophils, lymphocytes, and plasma cells. The alveolar spaces, alveolar duct (AD) and respiratory bronchiole (RB) are dilated associated with focal emphysema. PA: pulmonary artery; MB: membranous bronchiole.

patients with KS can be divided into three kinds of bronchiolitis: membranous, obliterative and respiratory. Airflow obstruction in these patients with KS could be derived from these changes of diffuse bronchiolitis.

On the other hand, histopathological findings of the diffuse centrilobular nodules in DPB corresponded to those of respiratory bronchiolitis, which showed thickening of the walls of the respiratory bronchioli with infiltration of lymphocytes, plasma cells and foamy macrophages without neutrophils associated with secondary ectasis of the proximal membranous bronchioli. The alveolar spaces were overinflated, but without emphysema [16, 17]. To demonstrate the differences between KS and DPB, the schematic reconstruction of the bronchiolitis in a case of typical

Fig. 8. – a) Walls of membranous bronchioli are thickened by infiltration of lymphocytes and plasma cells accompanied by intraluminal inflammation (patient 8, elastica van Gieson stain, Internal scale bar= 140 µm). b) Wall of a respiratory bronchiole is thickened by infiltration of lymphocytes and plasma cells accompanied by an accumulation of foamy macrophages (arrows) (patient 8, elastica van Gieson stain, Internal scale bar= 80 µm).

DPB is shown in figure 10. These characteristic histopathological features of DPB and the differences between DPB and OB have been demonstrated recently [18].

Thus, there were striking similarities between KS and DPB in clinical features, radiography images and pulmonary function tests; however, histopathological features obtained by reconstructing the lung specimens demonstrated distinct differences between these two diseases. The primary inflammatory lesions were in the membranous bronchioli in KS and in the respiratory bronchioli in DPB.

Recently, the mortality rate in patients with DPB has been markedly improved after the introduction of macrolide therapy for DPB in Japan [19, 20]. The mechanism by which macrolide therapy may have a remarkable effect on DPB would not be antibacterial but rather anti-inflammatory effects [21–23].

In this study, though macrolide was administered to all eight patients with KS, sputum volume, pulmonary function tests and radiography images were not affected, as described in a previous report [24]. Early antibiotic therapy, including quinolone, may be of benefit for superinfection and contribute to a favourable prognosis in KS.
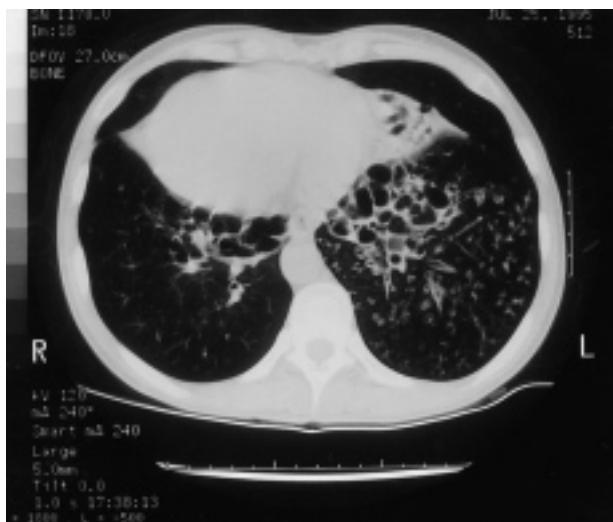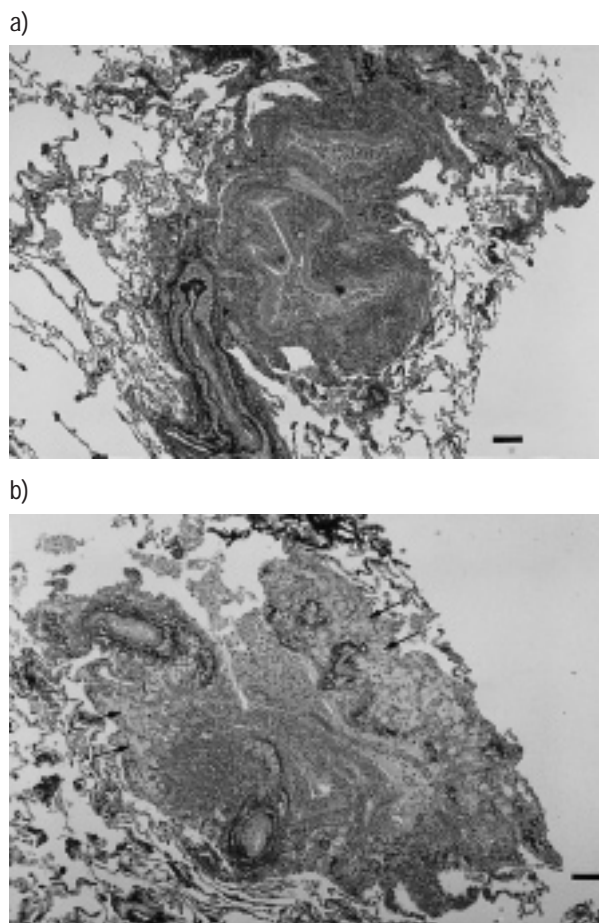

Fig. 7. – Chest computed tomography (CT) scan of patient 8 showing dextrocardia, bronchiectasis and diffuse centrilobular small nodules throughout both lungs.
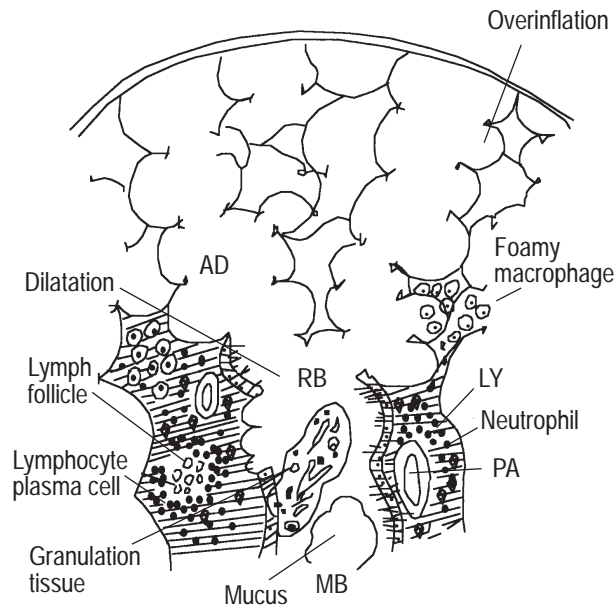
Fig. 9. – Schematic reconstruction of sections focused on the centrilobular lesions of patient 8 showing respiratory and membranous bronchiolitis associated with peribronchiolar fibrosis (▨), lymphoid hyperplasia (LY) and infiltration of neutrophils, lymphocytes, plasma cells and foamy histiocytes. The alveolar spaces, alveolar ducts (AD) and respiratory bronchiole (RB) are dilated. In the lumen of membranous bronchiole, granulation tissues and mucus are scattered. PA: pulmonary artery; MB: membranous bronchiole.

However, when a patient with progressed KS does not respond to antibiotics, lung transplantation may be the treatment of choice for such end-stage patients and has been applied to three patients with KS so far, as reported recently in the USA [25]. According to the current findings, it is suggested that the pathogenesis which produces centrilobular lesions is completely different between KS and DPB; the superinfection due to ciliary immobility in the former and the disturbance of immunological defense
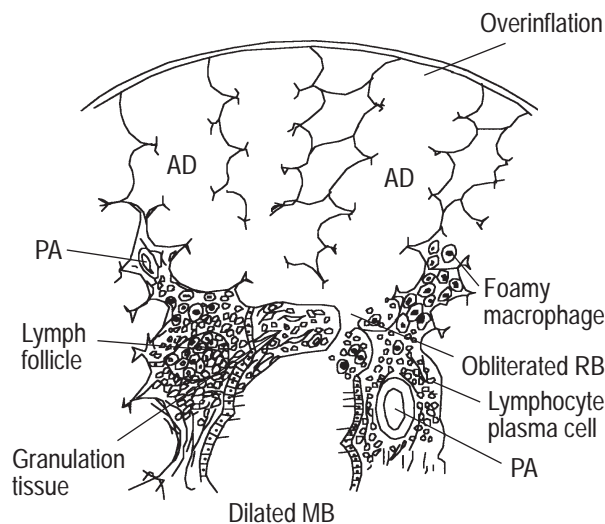

Fig. 10. – Schematic reconstruction of serial sections focused on the primary lesions in a case of typical diffuse panbronchiolitis, showing respiratory bronchiolitis and peribronchiolitis associated with ectasis of the proximal membranous bronchioli (MB). AD: alveolar duct; PA: pulmonary artery; RB: respiratory bronchiole.

mechanisms in the latter. Regarding this suggestion, VEV-AINA et al. [26] demonstrated that cilia exhibited complete absence of only the inner arms, while retaining the outer arms, and mucociliary clearance was totally absent, with normal neutrophil chemotaxis and other immunologic functions in a patient with KS.

It is concluded that the association of diffuse bronchiolitis might be one of the characteristic features of the lung in Kartagener's syndrome.

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