J Korean Med Sci 2001; 16: 150-4
ISSN 1011-8934

A Clinicopathologic Study on Three Cases of Constrictive Bronchiolitis

We describe the characteristic clinical and pathologic findings of three cases of constrictive bronchiolitis. All three patients were middle-aged women with chronic respiratory illness characterized by chronic cough, dyspnea, mild to severe obstructive pulmonary dysfunction, relatively normal chest radiographs with occasional peribronchial infiltration, and lack of response to bronchodilators or prednisolone. The patients also had medical diseases such as non-Hodgkin's lymphoma and hyperprolactinemia in case 1 and 3, respectively. None of the patients smoked cigarettes and had clinical evidence of recent viral lower respiratory tract infection. Histologic study by open lung biopsy revealed a spectrum of changes ranging from active cellular bronchiolitis to obliterative peribronchiolar fibrosis. The intervening interstitial and alveolar areas showed no remarkable lesion. Immunohistochemically, the bronchiolar or peribronchiolar inflammatory infiltrates mainly comprised of mixed T- and B-lymphocytes. It may be possible that the active form of constrictive bronchiolitis is initiated by attendant lymphocytic inflammation of the airways, which is followed by fibrous obliteration of bronchioles.

Key Words: *Bronchiolitis, Constrictive; T-Lymphocytes; Fibrosis*

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Received: 3 July 2000
Accepted: 26 December 2000

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INTRODUCTION

Constrictive bronchiolitis (CB) is a relatively rare disease which is characterized by obliteration of the lumina of bronchioles by inflammatory tissue elements and progressive destruction, eventually replaced by fibrotic tissue (1). Histologic features of CB can range from bronchiolar inflammation and minimal scarring, which are more prominent in the early stages, to considerable submucosal fibrosis encroaching upon the bronchiolar lumen, which is more frequently associated with advanced stage (2). Key histopathologic findings include constrictive narrowing of bronchiolar lumen, mural scarring, smooth muscle hyperplasia, and mucostasis. Conditions in which CB may be seen are as follows: healed infections (especially viral and mycoplasma), healed toxin or fume exposure; chronic bronchitis or emphysema, cystic fibrosis, and bronchiectasis; connective tissue disease; bone marrow or heart-lung transplantation; inflammatory bowel disease such as ulcerative colitis; drug reactions, e.g. penicillamine, *Sauropus androgynus* (3-8); and hematologic malignancy such as non-Hodgkin's lymphoma (9). However, the number of cases is limited and etiology and pathogenesis are not fully understood. Only a few studies suggest the possible relationship with immunologic response to yet unknown antigens (7-9).

The aim of this study is to describe the clinicopathologic findings of three women diagnosed as constrictive bronchiolitis with T-cell dominant lymphocytic infiltrates.

MATERIALS AND METHODS

Clinical studies

Medical histories and laboratory studies of the three patients were reviewed. Detailed medical histories recorded each patient's age, sex, occupation, and personal history of alcoholism, smoking, and allergies. Laboratory studies included serum immunological profiles, microbiological cultures and serological tests, imaging examinations such as chest radiographs and high-resolution computed tomography (HRCT) of lung, and pulmonary function tests. The three patients were clinically observed for the period ranging from 8 months to 4 yr to know

the disease progression.

Histologic and immunohistochemical studies

Histopathological analysis was performed on lung tissues sampled from three open lung biopsies. All tissues were fixed with 10% formalin and embedded in paraffin. The specimens were also inflated with 10% formalin before fixation; 5 μm-thick paraffin sections were cut and stained with hematoxylin and eosin.

Immunohistochemical stainings were carried out on paraffin sections by using the routine avidin-biotinylated peroxidase complex method. The primary monoclonal antibodies, such as CD3 (Novocastra, 1:100) for a T cell marker and CD20 (DAKO, 1:50) for a B cell marker, were used.

RESULTS

Clinical summary

The patients are all non-smokers and housewives (mean age, 47 yr). No history of drug ingestion or recent upper respiratory infections was found in the patients. Their associated diseases were malignant lymphoma of small B-lymphocytic type in the pelvic cavity of case 1 and hyperprolactinemia in case 3. Case 2 had no medical disease associated with CB except for a previous history of total thyroidectomy about 6 yr before the open lung biopsy. Their chief complaints were usually progressive dyspnea on exertion with or without cough. The duration ranged from 6 months to 10 yr. Auscultation revealed crackles in the lower lung fields in case 1 and 3 but clear breathing sound in case 2. Pulmonary function tests (PFT) disclosed mild to severe obstructive ventilation with no response to the bronchodilator (not done in case 1). These clinical characteristics of the three patients are summarized in Table 1, including physical and PFT findings.

Complete blood counts, C-reactive protein, erythrocyte sedimentation rate, total eosinophil count, and serum chemistry profile were normal, except for mild eosinophilia in case 1. The serum immunological profiles (including anti-nuclear antibody, rheumatoid factor, and quantitative analysis of serum immunoglobulins and complement) showed no abnormalities. Patients' sputa showed no growth of bacteria. Although chest radiographs were all essentially normal, HRCT of their lungs revealed bilateral bronchial wall thickening and dilatation and low-attenuation change of lung parenchyma (or hyperlucent lung), leading to a mosaic appearance (Fig. 1). All patients received bronchodilator and steroid (1 mg/kg body weight) therapy, but the respiratory symptoms and the subsequent PFTs were not improved. During the periods of clinical follow-up, case 1 expired 8 months after the diagnosis of malignant lymphoma and CB, and the conditions of case 2 and 3 were stationary, with the persistent respiratory symptom such as dyspnea on exertion.

Pathologic findings

Microscopic examinations of three open lung biopsies delineated a diagnosis of constrictive bronchiolitis, with some variable histologic findings among the three cases. Case 1 showed patchy involvement of bronchioles by concentric mural thickening and mild lymphocytic inflammatory cell infiltration. A bronchiole revealed near total obstruction with intraluminal crowded mucosal epithelia and marked submucosal fibrosis (Fig. 2). In case 2, several bronchioles were variably dilated or narrowed and

Table 1. Summary of clinical data in three patients

	Case 1	Case 2	Case 3
Age (yr) / Sex	47 / F	54 / F	41 / F
Chief complaint	Progressive DOE and chronic cough	Progressive DOE and mild cough	DOE
Duration	6 months	5 yr	10 yr
Occupation	Housewife	Housewife	Housewife
Smoking	None	None	None
Drug ingestion	None	None	None
Recent upper respiratory infection	None	None	None
Associated disease	NHL	None	Hyperprolactinemia
Chest auscultation	Crackles	Clear	Crackles
PFT *,†,‡	43.2 / 4.7 (100) / 24.8 (108)	68.9 / ND / 4.37 (89.9)	24.8 / 18.4 (85.4) / 18.7 (79.4)

DOE, dyspnea on exertion; NHL, non-Hodgkin's lymphoma; PFT, pulmonary function test; ND, not done
*: FEV1 (forced expiratory volume at one second)/FVC (forced vital capacity)
†: TLC (total lung capacity) (% predictability)
‡: DLCo (diffusion lung capacity) (% predictability)

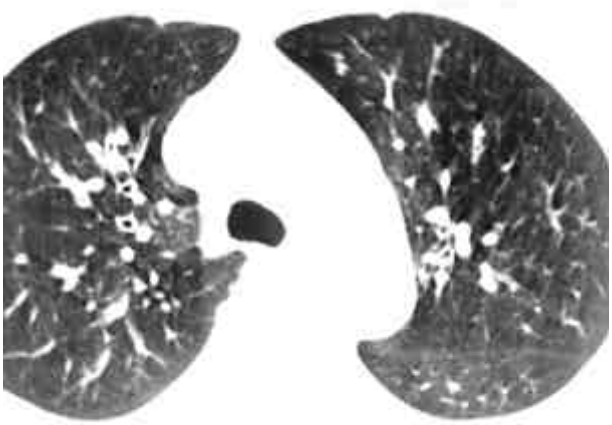

Fig. 1. HRCT of case 1 shows bilaterally diffuse bronchial wall thickening and mosaic pattern of heterogeneity of lung densities.

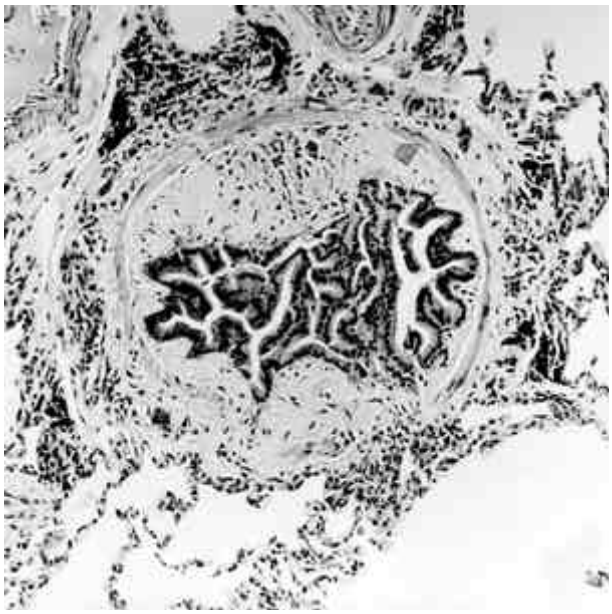

Fig. 2. Case 1 shows a typical histologic finding of obliterative bronchiolitis, which is characterized by the concentrically narrowed lumen filled with crowded mucosal folds and the submucosal fibrous thickening (H&E, ×200).

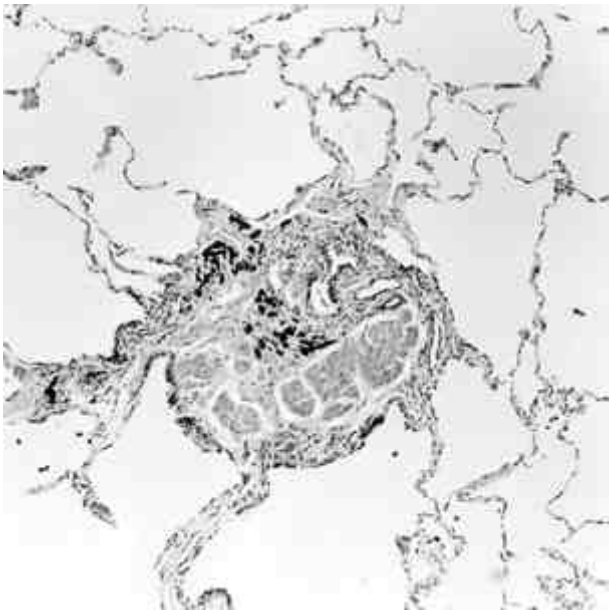

Fig. 3. A constrictive bronchiole of case 3 reveals a markedly narrowed lumen with submucosal fibrosis and adjacent normal lung parenchyma (H&E, ×100).

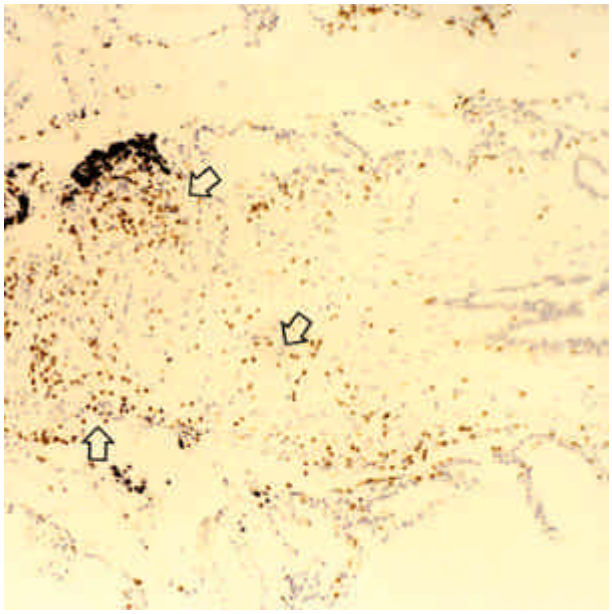

Fig. 4. Immunohistochemical staining for CD3, a T cell marker, discloses the dominant population of T lymphocytes (arrows) among the lymphoid infiltrates of a constricted bronchiole in case 1 (×200).

a bronchiole showed concentric narrowing, with submucosal fibrosis (Fig. 3). The submucosal areas of the dilated bronchioles disclosed mild lymphocytic infiltrates. No evidence of intraluminal fibromyxoid polyps was seen. In case 3, constrictive narrowing or secondary dilation of bronchiolar lumina was found, with mucostasis, submucosal fibrosis, and peribronchial inflammation. The submucosal inflammatory infiltrates were frequently dense, showing focal prominent eosinophil infiltration. Adjacent peribronchiolar interstitium showed mild lymphocytic inflammation, but the pulmonary parenchyma was otherwise normal. The immunohistochemical staining for CD3

Table 2. Summary of histopathologic and immunohistochemical findings

Case	Histology	Immunohistochemistry
1	Submucosal concentric fibrosis and luminal occlusion by crowded mucosal epithelia	T cell dominant lymphocytes
2	Dilated bronchioles with mucostasis or narrowed lumen with submucosal fibrosis and inflammation	T cell dominant lymphocytes
3	Narrowed or dilated bronchioles by heavy lymphoplasma cell infiltrates and submucosal fibrosis	T cell dominant lymphocytes

and CD20 revealed mainly CD3 (+) T lymphocytes and partly CD20 (+) B lymphocytes in all three cases (Fig. 4). These histopathologic and immunohistochemical findings are summarized in Table 2.

DISCUSSION

Bronchiolitis represents a response to injury and reflects an interplay of inflammatory cells and mesenchymal tissue, mainly involving bronchioles (3). The interplay between the cellular infiltrate and the mesenchymal reaction affects the lumen size, lamina propria, muscular layer, and bronchiolar adventitia. The distribution and the amounts of the cellular and mesenchymal components vary from case to case. Inflammation and fibrosis may be distributed in a nodular or a diffuse fashion along the airways, which may or may not be associated with luminal narrowing (3). Case 1 revealed a patchy involvement of the bronchioles by mainly concentric fibrosis with relatively sparse lymphocytic infiltration. Case 2 and 3 showed cellular bronchiolitis by lymphocytic inflammatory cells and mucin-filled dilated lumina. However, they commonly disclosed the distorted lumina with submucosal fibrosis and smooth muscle hypertrophy, leading to bronchiolar constriction. Constrictive bronchiolitis (CB) is a much less common pattern than a bronchiolitis obliterans organizing pneumonia (BOOP) pattern and usually a pure lesion of the bronchioles, with few changes in the distal parenchyma. CB refers to luminal narrowing by scarring rather than smooth muscle contraction. It can be distinguished from BOOP by no evidence of loose fibromyxoid intraluminal polyp. We did not find the intraluminal polypoid projection in all three cases, whereas the postinflammatory scarring and luminal constriction of the bronchioles were characteristically found.

CB is characterized by changes in the walls of terminal and respiratory bronchioles, often with few changes in alveolar ducts and alveolar walls (8). The histologic findings range from mild bronchiolar inflammation and scarring to progressive concentric submucosal fibrosis and occasionally, complete occlusion of the small airways. Other findings include smooth muscle hyperplasia, bronchioloectasia with mucostasis, and fibrosis of the small airway walls. It is unknown whether the variations in the morphology arise from the differences in the host immune response or from the diverse stages of tissue reaction (7). In all cases, the characteristic findings of CB were found, which included eccentric or circumferential submucosal inflammation and fibrosis and essentially normal peribronchiolar interstitium.

The clinical conditions in which CB may be seen are manifold (3-8), but our study revealed an unusual association of non-Hodgkin's lymphoma in case 1, which has been rarely reported worldwide only in a 38-yr-old Japanese woman with CB and paraneoplastic pemphigus (9). The authors interpreted the development of CB and paraneoplastic pemphigus as the facets of autoimmune responses associated with malignant lymphoma. The bronchioles in their study revealed submucosal and peribronchiolar fibrosis, with obliteration of the bronchiolar lumina and no inflammatory activity. In this study, our case 1 was a 47-yr-old woman with a huge pelvic mass which was diagnosed as malignant lymphoma of small B-lymphocytic type. She developed cough and dyspnea almost simultaneously. Open lung biopsy revealed markedly constricted bronchioles with submucosal fibrosis and focally scattered lymphocytes. Immunohistochemical study demonstrated the lymphocytes were mainly T-cell type, which were mixed with some B cells. We presumed that the lymphocytic response of CB would be related to the immunologic reaction to the non-Hodgkin's lymphoma. Case 2 had a thyroid disease of unknown diagnosis and underwent total thyroidectomy. Because the thyroid disease had developed about 6 yr before she was diagnosed as CB and there had been no symptoms related with thyroid dysfunction since that time, there seemed to be no relationship between the thyroid disease and CB in this case. Case 3 showed no clearly associated disease except for hyperprolactinemia which has not been known as the causative condition in literatures worldwide.

The most popular theory for the pathogenesis is that the entire spectrum of CB appears to be mediated by

a T-cell mediated process because most studies revealed that the predominant T-lymphocytic infiltrate preceded the peribronchiolar collagen deposition (7, 8). Our immunohistochemical study disclosed the staining pattern suggestive of the T-cell mediated pathogenesis, in that the peribronchiolar inflammatory infiltrates stained positive mainly for CD3, a T cell marker in all three cases. Eosinophils may collaborate with lymphocytes and other immunologic and mesenchymal cells to promote reactions ranging from the antigen-specific stimulation of lymphocytes to the induction of fibrosis (10). In case 3, the persistence of eosinophils in the fibrotic tissue of completely obliterated bronchioles may exhibit its collaborative role in the fibrotic process. Case 1 and 2 revealed no eosinophil infiltration in their tissues.

We report three cases of CB, a rare disease of small airways, who showed typical clinical and pathologic findings with an immunohistochemical staining result of T-cell dominant lymphocytic infiltrates.

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