Virchows Arch (1997) 431:275–282

ORIGINAL ARTICLE

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Broncho-bronchiolitis obliterans as a complication of bone marrow transplantation: a clinicopathological study of eight autopsy cases

Received: 14 January 1997 / Accepted: 5 March 1997

Abstract We identified eight patients with bronchiolitis obliterans (BO) in the autopsies of 81 bone marrow transplant (BMT) recipients. Rapidly progressive dyspnoea and cough were the main presenting symptoms in all eight patients, associated with overinflation and/or infiltrative opacity seen on chest X-ray and obstructive disorder revealed by pulmonary function tests. Early lesions were characterized by epithelial loss and an inflammatory infiltrate containing foamy histiocytes with mild luminal narrowing. Partial or total occlusion of the bronchiolar lumina by fibrous connective tissue was the feature of late lesions. Both changes were coexistent in all cases. In one case, small bronchi with cartilage were also affected by the obstructive process, showing bronchitis obliterans. All eight patients showed non-obstructive broncho-bronchiolitis characterized by denuding of respiratory epithelium, mural oedema and an inflammatory infiltrate in addition to BO, and these changes were also seen in 18 patients without BO. The submucosal glands of large bronchi and the trachea showed mucous retention and a mild inflammatory infiltrate in four of the eight patients. Coexistent infectious processes were seen in all cases, cytomegalovirus and Aspergillus being the most frequent organisms. BO probably develops as an immunopathological event related to graft-versus-host disease (GVHD) during the impaired immune status phase of the post-BMT period, possibly initiated by infection. Bronchial gland involvement in chronic GVHD is one of the factors responsible for this abnormal immune status.

Key words Bone marrow transplant · Bronchiolitis obliterans · Graft-versus-host disease · Bronchial gland

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Introduction

Bone marrow transplantation (BMT) is an effective treatment modality. Anti-leukaemic chemotherapy has recently advanced, with improved remission rates, but BMT is usually the only procedure for cases refractory to chemotherapy. Pulmonary complications, however, are often a serious problem in caring for BMT patients who are severely immunosuppressed until the immune function is recovered by transplanted bone marrow cells. In addition, the effects of immunosuppressive therapy and pre-BMT conditioning including chemotherapy and irradiation are important [1, 3, 5, 7–9, 11, 16, 17, 20, 21, 26, 37, 38]. During this vulnerable period, physicians are concerned about respiratory infections, which often lead to the patient's death despite intensive prophylaxis and treatment. Another major complication not directly related to infection is bronchiolitis obliterans (BO). This is clinically characterized by rapidly progressive dyspnoea and non-productive cough, overinflation on chest X-ray, and severe obstructive disorder refractory to bronchodilators revealed by pulmonary function tests (PFT) [3, 6, 9, 10, 17, 18, 23, 26, 27, 37, 38]. The discrepancy between the severe clinical symptoms and the subtle radiological findings, which are often underestimated or even

ignored, puzzles physicians and may result in delayed treatment.

Pathologically, bronchiolar changes vary from epithelial denudation and inflammation to partial or total obstruction of the lumen by fibrous tissue [10, 17, 37, 41]. In most patients disease progresses to a fatal outcome, although corticosteroid and other immunosuppressive agents are effective in a limited proportion of cases [9, 21, 26, 38]. Thus, this serious complication has become a target of interest for haematologists as well as pulmonologists. Although many investigators consider BO to be a pulmonary manifestation of chronic graft-versus-host disease (GVHD) [17, 29, 37, 41], the exact mechanism of the development of BO has not been elucidated. Selective involvement of bronchioles in this process may be due to anatomical or physiological reasons or to an immunological mechanism similar to that of the BO associated with heart-lung transplants (HLT) [28]. Changes in large bronchi and the trachea have been studied in combination with those in bronchioles, but no clear-cut relationship has been reported [1, 15, 22]. We studied eight autopsy cases of BO associated with BMT clinically and pathologically, in an attempt to elucidate the mechanism of development of BO with special reference to large airway pathology.

Materials and methods

During the period from 1974 to 1995, a total of 81 autopsies were performed from among more than 700 patients who underwent BMT for haematologic malignancies or other disorders in the Japanese Red Cross Nagoya First Hospital and Nagoya University Hospital. Clinical and autopsy protocols of these patients were reviewed. Ten to forty sections of the lungs per autopsy case were prepared for histological examination. Haematoxylin and eosin (H&E), and elastic Masson Goldner (EMG) staining was prepared for all cases, whereas Grocott methenamine silver, Brown-Hopps, and Giemsa stainings were used in cases in which infectious processes were used in cases in which infectious processes were suspected. The leading pulmonary alteration in the 81 autopsy cases was infection (69%), especially with cytomegalovirus (CMV; 38%) and *Aspergillus* (20%). Among non-infectious processes, diffuse alveolar damage (DAD; 41%) and bronchiolitis without obstruction (21%) were commonly seen. Eight cases of BO were selected from 81 autopsy cases based on the presence of pathologically recognized bronchiolar lesions with luminal occlusion, partial or total; these became the subjects for further investigation in this study. The degree and extent of inflammatory infiltrate and fibrosis, both mural and luminal, in the small bronchi and bronchioles were semiquantitated in the eight cases as none, mild, moderate, and marked, as were additional findings including interstitial fibrosis and inflammation and nuclear inclusions. Large bronchi and the trachea were also carefully observed, with special attention paid to changes in bronchial and tracheal glands in five cases; the examination was limited to segmental bronchi in the other three. Clinical and radiographical data of these cases, including the patient profile, clinical history, and chest X-ray and computed tomography (CT) scan, were also reviewed and summarized with special attention to respiratory symptoms and signs.

Results

The clinical data on the eight patients with BO are summarized in Table 1. The patients included five men and three women, aged 6–46 years (mean, 30). All patients received allogeneic BMT with conditioning regimens consisting of total-body irradiation and cyclophosphamide with or without busulfan or cytosine arabinoside. Immunosuppressive agents were administered to all patients after BMT, including methotrexate with or without cyclosporine A as prophylaxis for GVHD and prednisone with or without cyclosporine A as treatment for GVHD. The onset of respiratory disease was 110–430 days after BMT, with symptoms including non-productive cough (7/8), dyspnoea (5/8), fever (2/8), chest pain (1/8) and pneumothorax (1/8). Radiological studies revealed overinflation, interstitial opacity or pneumonic shadows, individually or in combination. PFTs were performed in four cases and revealed an obstructive disorder in two and a combined obstructive and constrictive disorder in two. Infection by CMV, varicella zoster virus (VZV) or mycobacterium tuberculosis was evident before death in five, one, and one cases, respectively, on microbiological or serological examination. By transbronchial lung biopsy, BO was suggested in only one case (8); the others showed non-specific interstitial pneumonia or drug-induced eosinophilic pneumonia. Seven patients died of progressive respiratory failure 27–1907 days after the onset of respiratory symptoms, while relapse of acute leukaemia led the other patient's death 99 days after the onset of respiratory symptoms that became unremarkable just before death.

The airway lesions in eight cases with BO were evaluated with particular attention to the degree and extent of the inflammatory infiltrates and fibrosis, which are summarized in Table 2. Membranous and respiratory bronchioles of about 100–500 μm in diameter were affected with inflammatory and/or fibrotic processes in all cases, and in case 8 small bronchi were also involved. Bronchiolar lesions in each case varied from early inflammatory changes to the late scarring state. The early lesions were characterized by sloughing of respiratory epithelium, fibrinous exudation, inflammatory infiltration and collections of foamy macrophages within the lumina, and mild oedema and fibrosis in the wall (Fig. 1). The luminal occlusion was mild. An inflammatory infiltrate was generally mild and largely lymphoplasmacytic, although neutrophils predominated in three cases. The main feature of late lesions was total or partial obstruction of the bronchiolar lumen by dense fibrosis with minimal inflammation (Figs. 2, 3). Totally occluded bronchioles were recognized only with the location adjacent to the pulmonary artery, the circumferential muscular layer, and their outlines which were highlighted by EMG stain (Fig. 2). The remaining lumen was lined by regenerating respiratory epithelium in partially occluded bronchioles (Fig. 3). In all cases, bronchiolar changes of various stages were simultaneously present, although old lesions were prevalent in some cases and early lesions predominated in others. Collections of foamy macrophages and organizing fibrosis in distal airspaces were observed in case 2, showing the bronchiolitis obliterans organizing pneumonia (BOOP) pattern. In case 8, small bronchi, which con-

Table 1 Summary of clinical findings in eight patients (*AML* acute myelogenous leukemia, *ATL* adult T-cell leukemia, *ALL* acute lymphatic leukemia, *BMT* bone marrow transplant, *CY* cyclophosphamide, *TBI* total-body irradiation, *CA* cytosine arabinoside, *BU* busulfan, *TLI* total lymphoid irradiation, *RS* respiratory symptoms, *CXR* chest X-ray, *PFT* pulmonary function test, *TBLB* transbronchial lung biopsy, *EP* eosinophilic pneumonia, *IP* interstitial pneumonia, *CMV* cytomegalovirus, *VZV* varicella-zoster virus)

Case	Age	Sex	Primary disease	preBMT regimen	Respiratory symptoms	Onset of RS post-BMT (days)	CXR	PFT	TBLB	Infection	Survival post onset of RS (days)	Outcome
1	6	F	AML	CY, TBI	Cough, dyspnoea	110	Pneumonic shadow, effusion	Not done	Not done	CMV	52	Died of respiratory failure
2	43	M	ATL	CY, TBI	Cough	164	Interstitial opacity	Obstructive disorder, mild	EP, IP	CMV	42	Died of respiratory failure
3	14	M	ALL	CY, CA, TBI	Cough, fever	120	Interstitial opacity	Not done	Not done	CMV	142	Died of respiratory failure
4	40	M	Erythro-leukemia	CY, TBI	Cough, dyspnoea	276	Interstitial opacity	Not done	IP	VZV	27	Died of respiratory failure
5	25	M	ALL	CY, TBI	Cough, dyspnoea, pneumothorax	161	Overinflation, pneumonic shadow	Combined disorder	IP	Tuberculosis	1907	Died of respiratory failure
6	46	M	AML	CY, BU, TBI	Cough, fever chest pain	201	Pneumonic shadow	Not done	Not done	CMV	99	Died of relapse of AML
7	28	F	AML	CY, TBI	Cough, dyspnoea	430	Overinflation, reticulonodular	Obstructive disorder	Not done	None	366	Died of respiratory and renal failure
8	38	F	AML	CY, BU, TLI	Dyspnoea	430	Overinflation	Combined disorder	S/o bronchio-litis obliterans	CMV	64	Died of respiratory failure

Table 2 Summary of pathological findings in eight patients (*GVHD* graft-versus-host disease, *DAD* diffuse alveolar damage, – none, + mild, 2+ moderate, 3+ severe)

Case	Bronchioles (and small bronchi[b])								Bronchial gland		Chronic GVHD	Other findings
	Fibrinous exudate	Epithelial sloughing	Neutrophilic infiltrate	Lymphocytic infiltrate	Foamy histiocytes	Luminal fibrosis	Mural fibrosis	Muscle hyperplasia	Lymphocytic infiltrate	Mucus retention		
1	2+	2+	3+	2+	–	+	+	+	2+	+	Liver, skin, mouth	DAD, bacterial pneumonia
2	2+	2+	+	+	–	2+	+	+	+	+	None	OrgDAD, haemorrhagic pneumonia, VZV, CMV
3	+	2+	2+	+	+	+	+	+	–	–	Liver, skin, mouth, eyes	Alveolar infiltrate of foamy macrophages
4	+	2+	–	+	+	2+	+	–	+	2+	Liver, skin, mouth, eyes	DAD, aspergillus, VZV
5	+	2+	2+	–	3+	+	2+	–	–	–	Liver, skin, mouth, eyes,	Bacterial pneumonia, interstitial pneumonia
6	–	+	–	+	3+	3+	2+	–	–	–	Liver, skin	Haemorrhage, nocardia
7	+	+	–	+	2+	3+	2+	–	–	–	Liver	CMV
8[a]	+	2+	–	+	2+	2+	3+	+	+	2+	Liver, skin, mouth, eyes	DAD, CMV, aspergillus, haemorrhagic infarct

[a] Changes listed here in small bronchi as well as bronchioles
[b] Examination of large airway was limited up to segmental bronchi in cases 5–7

Fig. 1 Case 6. The bronchiolar epithelium is focally desquamated with an aggregate of foamy macrophages and lymphocytes, which partially occludes the lumen. H&E stain, ×40

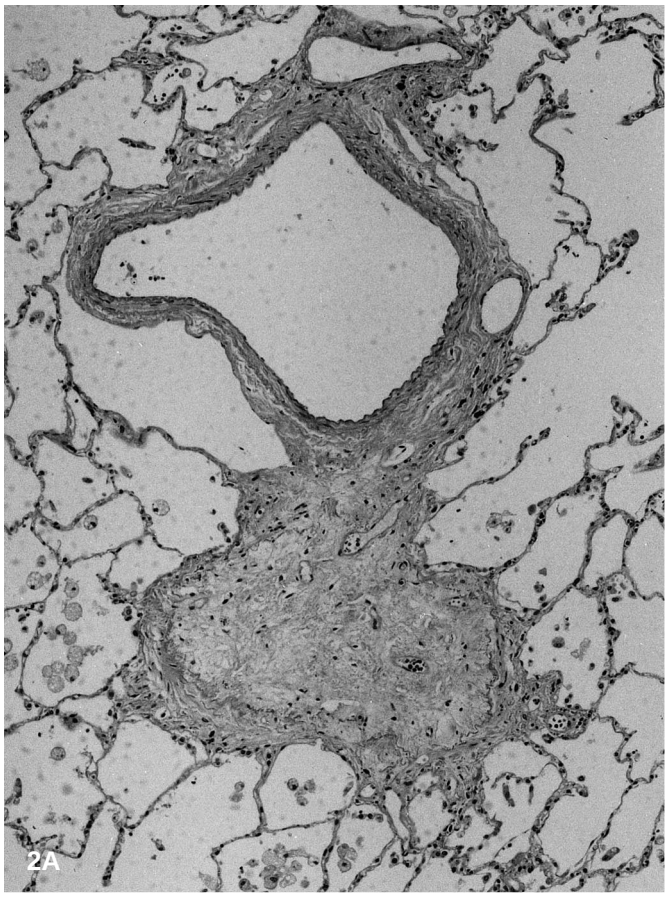
tain cartilage in their wall, also occasionally disclosed either sloughing of respiratory epithelium with fibrinous exudate, mural infiltrate of lymphocytes and plasma cells, or obliteration of the lumina by fibrous granulation tissue (Fig. 4).

In five of the eight cases, submucosal glands in large bronchi and trachea show mucus retention within acini lined by atrophic cells, an infiltate of lymphocytes and plasma cells, and sloughing of surface epithelium with subepithelial fibrosis (Fig. 5).

All eight patients showed non-obstructive inflammatory changes in bronchioles and bronchi together with BO, which were seen also in 18 patients without BO. Those lesions were characterized by sloughing of respiratory epithelium, mural oedema and an infiltrate of lymphocytes and plasma cells with neutrophils.

Fig. 2 Case 7. A totally occluded bronchiole is recognized as a scarring lesion adjacent to a pulmonary artery. Inflammatory infiltrate is minimal. Elastic staining highlights the outline of the bronchiolar wall. **A** H&E, **B** EMG, ×40 ▶

Fig. 3 Case 6. A bronchiole is largely occluded by fibrous tissue with a small lumen lined by ciliated respiratory epithelium. **A** H&E, **B** EMG, ×40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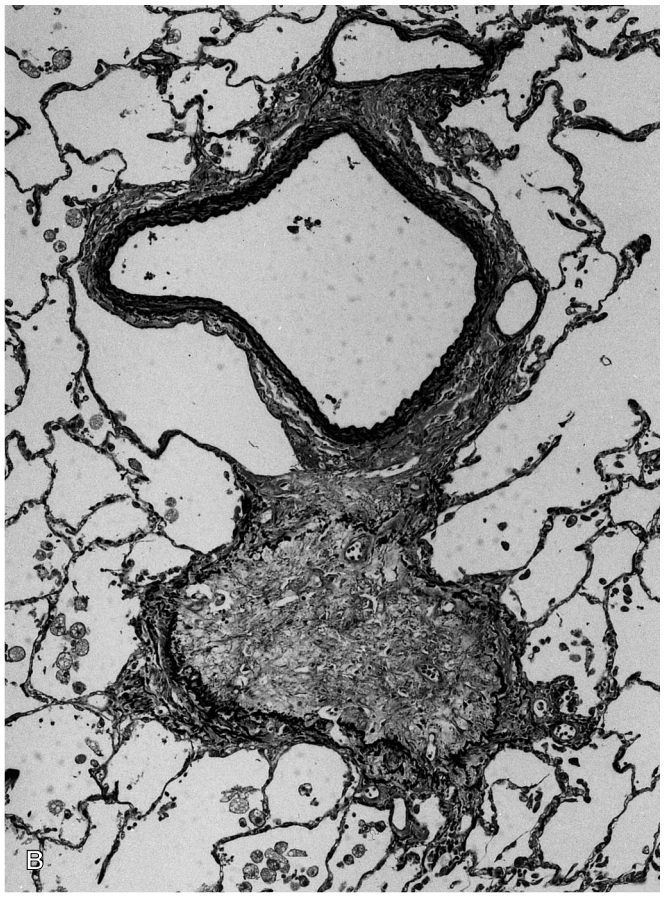
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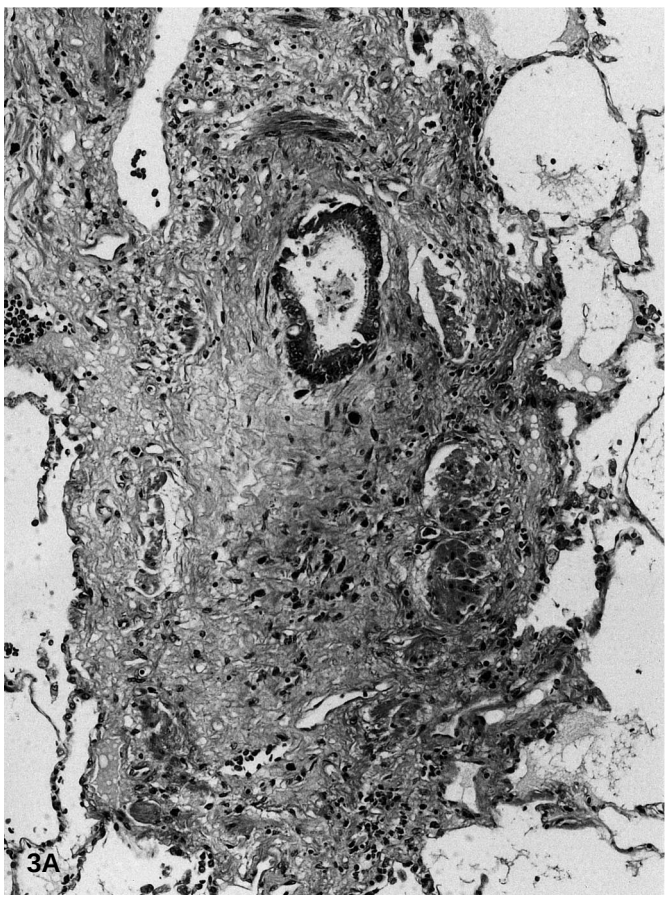
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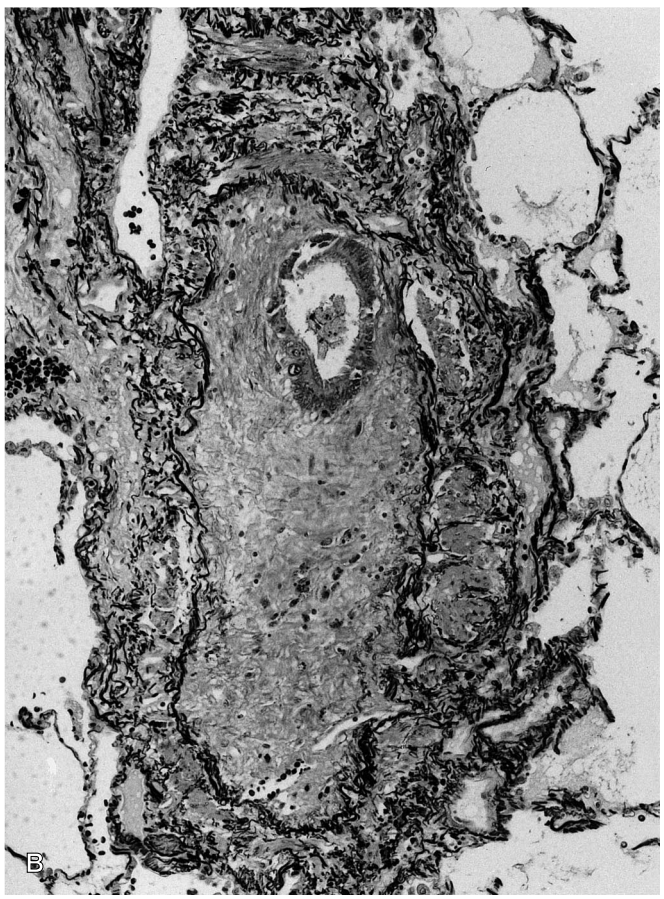
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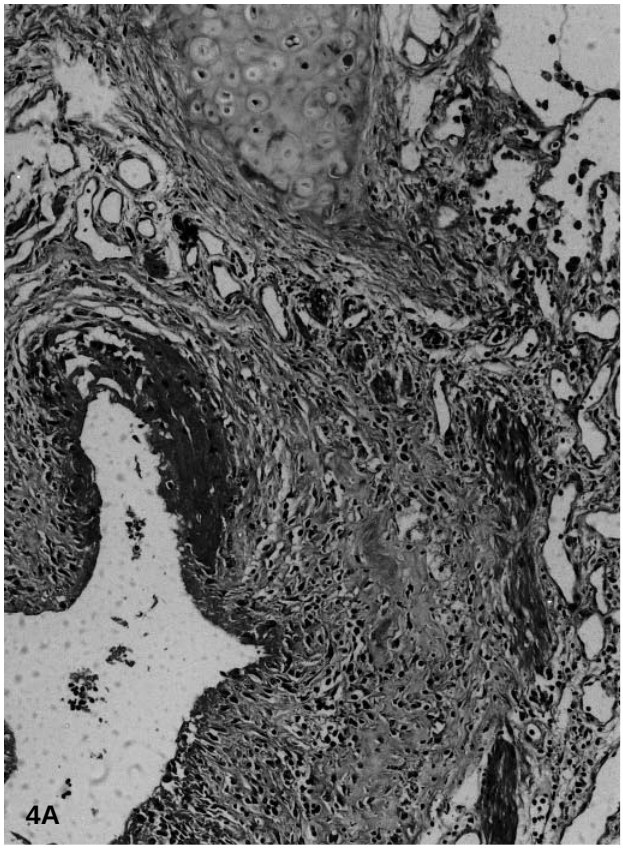
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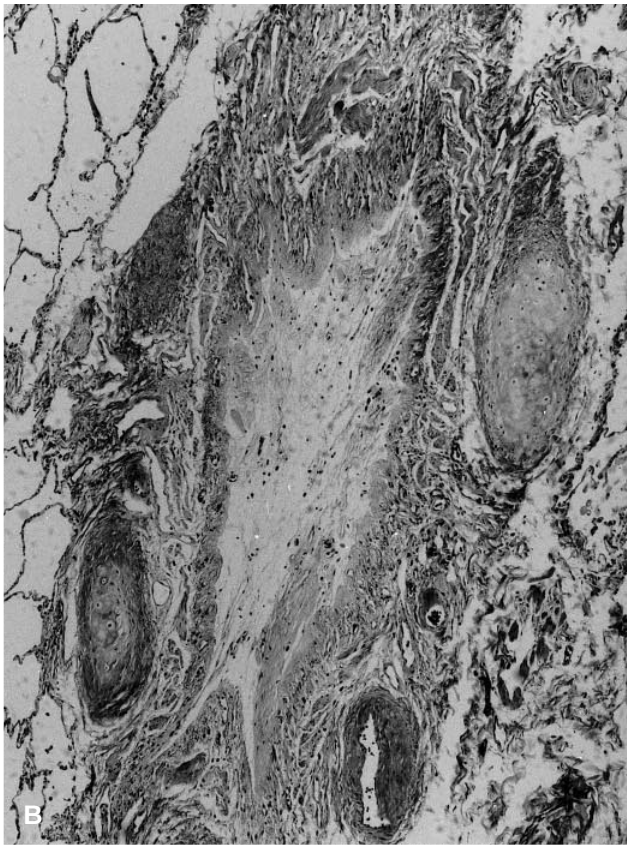
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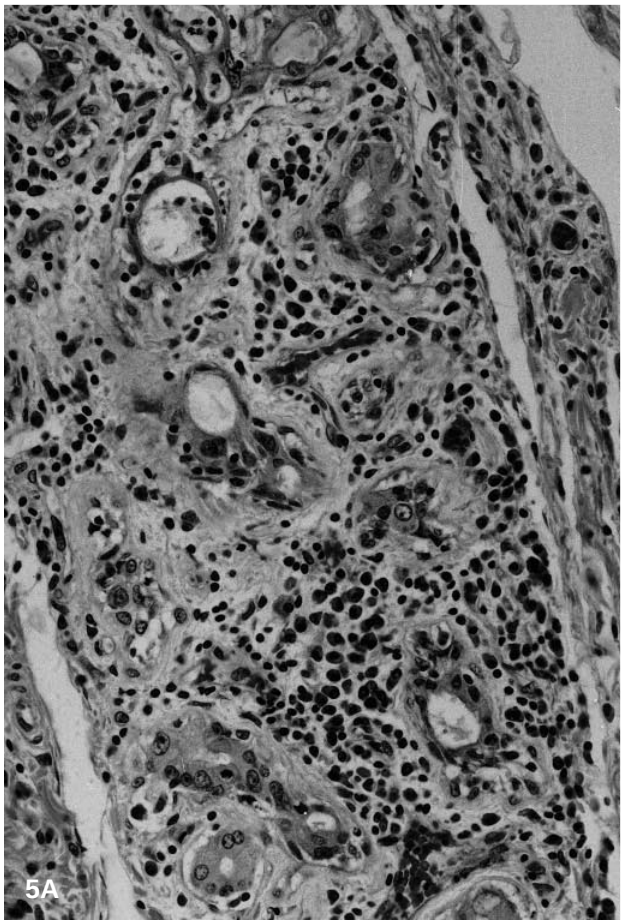
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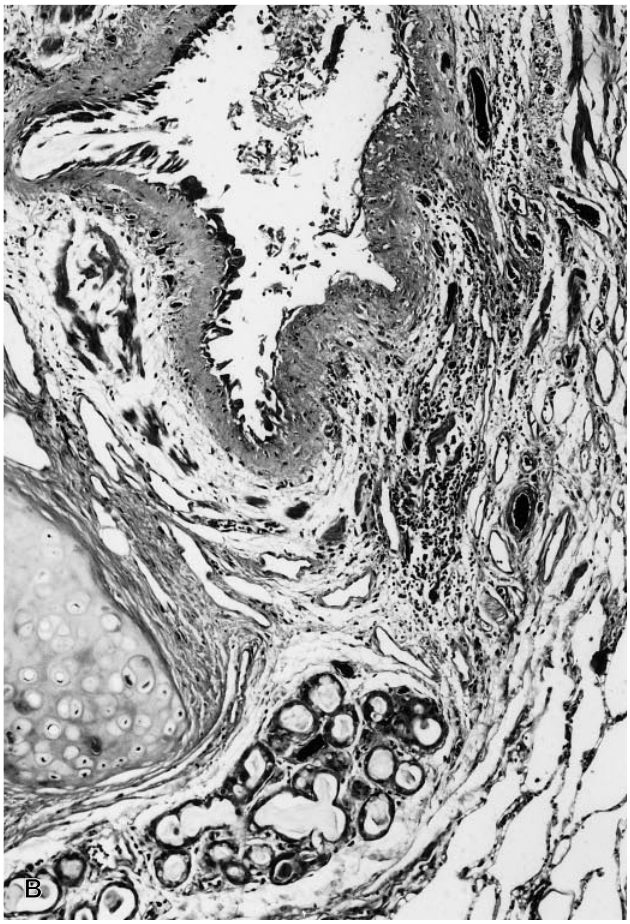
B

Infections by viruses, fungi and bacteria were seen in seven of eight cases, while DAD was another common accompaniment (4/8). Non-specific interstitial fibrosis and inflammation were also seen in some areas. In all but one case of BO, chronic GVHD was observed in skin, liver, eyes, mouth and salivary glands.

Discussion

Chronic GVHD is a late complication of allogeneic BMT, involving systemic organs including skin, liver, minor salivary glands, mouth, eyes, and the musculoskeletal system [12, 13, 30, 31, 32]. It remains controversial whether or not BO is a pulmonary manifestation of chronic GVHD, although the majority of previous reporters have favoured this idea [20, 26]. Most patients with BO associated with BMT have chronic GVHD in other organs [3, 17, 27, 31, 37, 38], as was the case in all but one of our cases. In addition, decreased airflow rate was observed in the majority of GVHD patients with effective prophylaxis by cyclosporine A [6, 24]. However, another mechanism for the development of BO has also been proposed on the basis of bronchoalveolar lavage analysis of BMT patients and the occurrence of BO associated with autologous BMT [25, 33]. In addition, BO was found in one of our patients who had died of relapsed AML, which is unlikely to occur in patients with GVHD because of so-called graft versus leukaemia effect. We thought that BO in this case, which was histologically in the old scarring state, may have developed long before the leukaemic relapse, which occurred after the GVH reaction diminished.

Yousem [41] has recently classified pulmonary GVHD by an integrated assessment of clinical and pathological features of BMT patients who had undergone open biopsy. He has categorized pulmonary GVHD into four major patterns; DAD, lymphocytic bronchitis/bronchiolitis with interstitial pneumonia, BOOP, and cicatricial BO. These patterns are thought to occur in sequence or in combination, disclosing the complex histology for pulmonary GVHD. The pulmonary changes in our patients were, for the most part, in keeping with the Yousem's criteria. In particular, the bronchiolar changes from early exudative to late scarring phases were comprehensible with reference to his theory on the developmet of airway lesions in pulmonary GVHD. In addition to his guideline, we might emphasize two points; the occurrence of luminal occlusion in small bronchi as well as in the bronchioles, and the significance of bronchial gland involvement by GVHD in the development of airway injury.

◀ **Fig. 4A** Case 8. A bronchus with a fragment of cartilage in its wall shows partial occlusion by inflammatory granulation and fibrinous exudate. Epithelium is entirely denuded. H&E, ×100. **B** Case 8. Another small bronchus is entirely occluded by myxomatous connective tissue. Inflammatory infiltrate is mild. H&E, ×40

Fig. 5A Case 2. Bronchial gland shows a lymphoplasmacytic infiltrate with atrophy of acinar cells. H&E, ×200. **B** Case 8. A small bronchus shows epithelial sloughing and subepithelial fibrosis, as well as mucus retention in bronchial glands. H&E, ×100

It is known that the minor salivary glands are frequent targets of chronic GVHD [31]. In tracheal and bronchial glands, which are similar in morphology and function to the salivary glands and have a common embryological origin, chronic GVHD might be expected to occur. In fact, the frequent occurrence of lymphocytic bronchitis involving submucosal glands has been reported in patients with chronic GVHD in other organs, suggesting the possible association with small airway alterations [1, 17, 30, 36]. Yousem [40] also suggested that large airway inflammation is a good marker for small airway disease in HLT patients, in which the histology is similar to that associated with BMT. In contrast, large airway inflammation was not considered to be particularly indicative of GVHD by some investigators [15, 22]. Our results indicate that chronic GVHD of large airways, especially of the submucosal glands, is one of the factors associated with development of BO. Our speculation is as follows: secretions of the bronchial glands coat the surface of the bronchi and distal bronchioles, and play an important role in defence mechanism. Impaired secretion by bronchial glands results in increased vulnerability to various insults in the distal airway. When the dysfunction is mild, damage will be seen only in the most distal bronchioles, which are least protected by the secretion. In contrast, when the bronchial glands are severely impaired by GVHD, the distal airway will be more extensively affected, possibly up to the broncial level, as seen in case 8. Thus, BO, and broncho-bronchiolitis obliterans are considered to be due at least in part to GVHD of the bronchial glands in the proximal bronchi and trachea. Of course, we do not attribute bronchiolar lesions in all cases to the bronchial gland dysfunction, because some of our cases showed almost normal glands. The pulmonary mucociliary defence system can be injured at any level of the airway and to varying extents by GVHD.

Although cases of BOOP have been reported to be a complication of BMT [35, 41], BO without organizing pneumonia is more prevalent in BMT. Selective bronchiolar involvement is commonly seen in the lungs of BMT and HLT patients [34, 39]. In HLT patients, small airway injury as a manifestation of acute rejection is thought to be a harbinger of BO (Yousem) [40]. The expression of class II major histocompatibility antigens by bronchial epithelium is also thought to be closely associated with acute rejection in lung allografts [2, 28]. Bronchioles may be readily injured by both rejection and GVHD not only because of the mechanical weakness but of the specific immunological responses involved. Brochiolitis with similar features to the BMT-associated form is also seen in patients with collagen-vascular diseases (CVD) [14, 19], some of which resemble chronic GVHD both clinically and pathologically [12, 13, 30, 32].

It is still a matter of controversy whether development of BO in BMT patients is associated with infectious events or not, although a substantial percentage of BO cases show negative results in culture or special staining of the open biopsy specimen [37, 41]. Infection may be the initial insult in the development of BO, complicated by a poor resolution and subsequent progression of fibro-

sis in the abnormal immune status. In this regard, non-obstructive bronchiolitis in 18 of our 81 autopsy cases may reflect either the persistent inflammatory status or pre-BO status initiated by an infection.

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