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Bronchiolitis obliterans in ataxia-telangiectasia

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Abstract Pulmonary disease was studied in four patients with ataxia-telangiectasia. Immunodeficiency was characterized by lymphopaenia, hypo-gammaglobulinaemia and decreased T-cell response to phytohaemagglutinin stimulation in mixed lymphocyte cultures. All four patients died from respiratory failure. Autopsy revealed that all four patients suffered from bronchiolitis obliterans in all lobes. Immunohistochemical examination demonstrated expression of MHC class II antigens on bronchiolar epithelium. Pulmonary infections in ataxia-telangiectasia patients included a case of mycoplasma pneumonia, one of cytomegalovirus pneumonia and one of *Pseudomonas aeruginosa* infection. The aetiology and immunological background of bronchiolitis obliterans are discussed. Bronchiolitis obliterans is a characteristic finding in ataxia-telangiectasia and may be due to the underlying immune deficit.

Key words Bronchiolitis obliterans · Ataxia-telangiectasia · Mycoplasma · MHC class II

Introduction

Ataxia-telangiectasia is an autosomal recessive genetic disease characterized by cerebellar ataxia, oculocutaneous telangiectasia, variable levels of T-cell immunodeficiency, and the inability to repair radiation induced damage to DNA. Nonrandom chromosomal translocations and lymphoid neoplasia are frequent events [3, 9]. As in other immunodeficiencies, recurrent sinopulmonary infections and tumours are the most common causes of death [3]. Ataxia-telangiectasia patients have functional and numerical T-cell defect and selective immunoglobulin deficiencies, especially of IgA and IgE [3].

The mucosal defence system of the lung is generated by the bronchus-associated lymphoid tissue [2]. The secretory IgA system also is an important factor in mucosal immunity with an IgA response to luminal antigen playing a key role in the initial control of microbial colonization [17]. However, a recent study of T-cell responses to inhaled antigens and the capacity of $CD4^+$ T-cells to transfer immunity [29] suggests T-cells may control infections involving persistent microbes or those involving inhalation of a large inoculum of antigen [25]. Although other mechanisms, such as secretion of lactoferrin (Lf) and lysozyme (Lz) from macrophages, have been implicated [8] in the control of pulmonary infections, we speculated that IgA deficiency and T-cell dysfunction in ataxia-telangiectasia patients may lead to a characteristic pattern of pulmonary disease.

In this study, we examined the pulmonary pathology in ataxia-telangiectasia patients. We found that bronchiolitis obliterans was a characteristic feature of their pulmonary disease and examined the immunophenotypic changes in bronchiolar epithelium and identified characteristic infectious agents.

Materials and methods

Primary immunodeficiency diseases in the Nagoya University Hospital autopsy record from 1980–1995 were reviewed.

Multiple tissue samples were obtained from all lobes and were fixed in 10% buffered formalin and embedded in paraffin. Sections were stained with haematoxylin and eosin, periodic acid-Schiff, elastica Masson, and other stains as appropriate, including methenamine silver, Gram and Ziehl-Neelsen stains.

Antibodies directed against infectious agents, lymphocyte markers and immunoglobulins were as described in Table 1. Paraffin embedded tissue sections were stained using the labelled streptavidin-biotin-peroxidase technique. Briefly, tissue sections were deparaffinized and digested with trypsin as needed for primary antibodies, as shown in Table 1. Primary antibodies were applied overnight at 4°C. Tissue sections then were treated with hydrogen peroxide in methanol and incubated sequentially in secondary antibody (biotinylated goat anti-mouse or -rabbit immunoglobulins)

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Table 1 Antibodies and antisera used for immunohistochemistry (*RA* rabbit antiserum, *mAb* mouse monoclonal antibody, *TCR* T-cell receptor, *HA* human antiserum, *GA* goat antiserum, *kDa* kilodalton, *HRP* horse radish peroxidase)

Antibodies	Type	Source	Dilution	Specificity
CD 3	RA[a]	DAKO patts	1:100	CD3, pan T-cells
L-26	mAb	DAKO patts	1:200	CD20, pan B-cells
TCR-β	mAb	T Cell Science	1:20	TCR β chain
UCHL-1	mAb	DAKO patts	1:300	CD45RO, pan T-cells, granulocytes and monocytes
LN-3	mAb	Biotet Diagnostic	1:50	HLA-DR, monocyte/macrophage, activated T and B-cells
S-100	RA	DAKO patts	1:400	S-100 protein
KP-1	mAb	DAKO patts	1:200	CD68, monocyte/macrophages
Ig G	RA[a]	DAKO patts	1:800	Ig G
Ig M	RA[a]	DAKO patts	1:800	Ig M
Ig A	RA[a]	DAKO patts	1:400	Ig A
Secretory component	RA	DAKO patts	1:600	Secretory component
Lactoferrin	RA	DAKO patts	1:600	Lactoferrin
Lysozyme	RA	DAKO patts	1:800	Lysozyme
CMV(CCH2)	mAb	DAKO patts	1:100	Cytomegalovirus (CMV) antigen (76 kDa)
RSV	RA	DAKO patts	1:200	Respiratory syncytial virus (erv) antigen
Mycoplasma	HA		1:5000	Anti-mycoplasma human serum
Biotin anti mouse immunoglobulins	RA	DAKO patts	1:300	
HRP-streptoavidin		Histoclone	1:100	
HRP-anti rabbit immunoglobulins	GA	MBL	1:100	
HRP-anti human immunoglobulins	RA	DAKO patts	1:50	

[a] Digestion in 0.1% trypsin at 37° C for 30 min was carried out before staining

Table 2 Clinical features of four patients with ataxia telangiectasia (*F* female, *M* male, *T-ALL* T-cell acute lymphoblastic leukaemia)

Case number	Sex/Age (years)	Age at diagnosis (years)	Age at onset of respiratory symptoms (years)	Telangiectasia	Other manifestations	Affected relatives
1	F/20	1	17	+		Sister, uncle
2	M/14	2	14	+	T-ALL	Sister
3	M/20	6	10	+		Brother
4	F/15	9	9	+		–

and streptavidin peroxidase. Chromogenic development was accomplished by immersion in a solution of 3, 3'-diaminobenzidine hydrochloride, followed by counterstaining with haematoxylin.

Detection of mycoplasma antigens was performed using a human convalescent serum, obtained from a patient with mycoplasma pneumonia and a high serum titre of anti-mycoplasma antibody (> 1:5000), as primary antibody. Following mycoplasma antibody treatment tissue sections were blocked for endogenous peroxidase activity and incubated with horseradish peroxidase conjugated anti-human immunoglobulins. Chromogenic development and counterstaining were performed as described above. Positive and negative controls used were the paraffin sections of mycoplasma bronchitis and normal lung tissue from autopsy cases.

Results

Nine primary immunodeficiency diseases, including four patients with ataxia-telangiectasia, two with severe combined immunodeficiency, one X-linked agammaglobulinaemia, one X-linked hyper IgM syndrome and one Nijmegen breakage syndrome, were registered in the Nagoya University Hospital autopsy record.

The clinical features of ataxia-telangiectasia are summarized in Tables 2 and 3. The four patients with ataxia-telangiectasia comprised two men and two women ranging in age from 14 to 20 years (median age, 17.5 years) at autopsy. All four had progressive cerebellar ataxia and oculocutaneous telangiectasia. Three patients had a family history of ataxia-telangiectasia. Case 2, a 14-year-old boy, was diagnosed with T-cell acute lymphoblastic leukaemia and obtained complete remission 2 years after diagnosis. Recurrent respiratory infections then occurred, with a delay in the initial diagnosis of ataxia-telangiectasia. Clinical symptoms were severe dyspnoea with abundant sputum production in all cases except for case 2. Respiratory failure was the cause of death of all four cases.

Laboratory data showed mild to severe hypogammaglobulinaemia, with especially low serum concentrations of IgA in all cases. With regard to T-cell function, reactivity to phytohaemagglutinin (PHA) was very low in all cases. Case 1, a 20-year-old woman, showed recurrent elevation of anti-mycoplasma antibody.

Table 3 Laboratory findings in four patients with ataxia telangiectasia (*WBC* withe blood cell count, *γ-gl* serum gamma globulin (g/dl), *CHA* cold haemagglutinin, *ND* not done

Case number	WBC	γ-gl	Ig G	Ig M	Ig A	Peripheral lymphocytes			CHA	Anti-Myco-plasma	Anti-CMV
						Total	T-cell	B-cell			
1	5200	1.3	1460	360	140	2100			128	320	ND
2	5200–10500	1.7	700	82	160	650–1250			1024	ND	ND
3	5500–12800	1.0	982	309	<35	1600–3600	34%	7%	>1024	<40	<4
4	6900–32600	1.3	1430	267	15	1100–2200	62%	4%	512	ND	<4

Table 4 Pathologic features of the lungs in four patients with ataxia telangiectasia

Case number	Weight (g) Left/Right	Bronchiolitis	Organizing pneumonia	Broncho-pneumonia	Pulmonary fibrosis	Emphysema	Infectious agents
1	200/220	Bil diffuse	Focal	–	Bil LL	Bil LL mild	*Mycoplasma pneumoniae*
2	170/230	Bil diffuse	Focal	–	–	–	CMV
3	270/410	Bil diffuse	Focal	RLL	Bil UL, LL	Bill LL severe	
4	235/300	Bil diffuse	Focal	RLL	Bil LL	Bil LL severe	*Pseudomona aeruginosa*

Serum cold haemagglutinin concentrations were elevated in all cases. Respiratory function tests were not carried out.

The other five patients with primary immunodeficiency were a 1-year-old boy and 1-year-old girl with severe combined immunodeficiency, a 16-year-old boy with X-linked agammaglobulinemia, a 10-year-old boy with the X-linked hyper IgM syndrome and a 4-year-old boy with Nijmegen breakage syndrome.

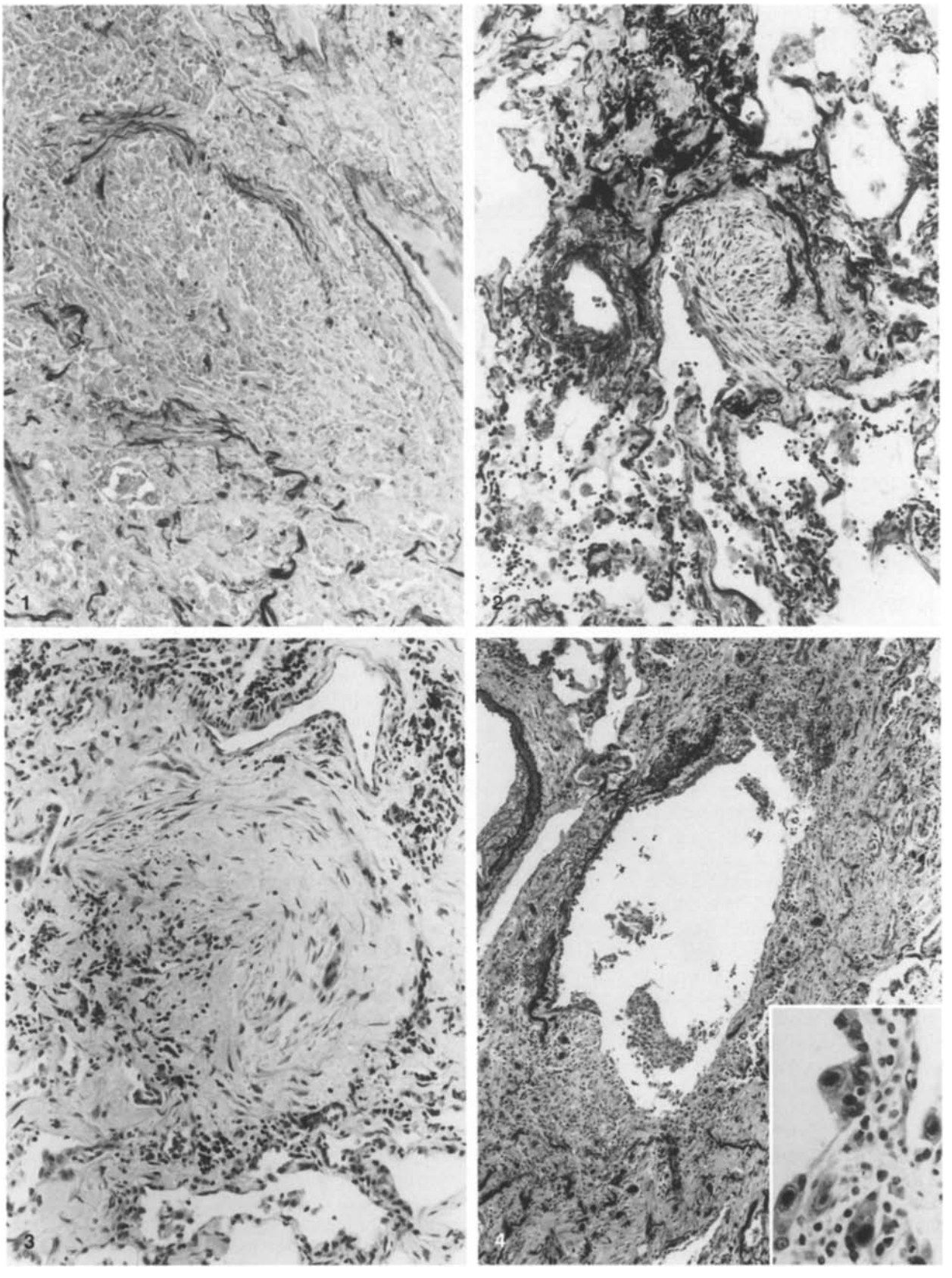
Pathological changes in the lungs in the ataxia-telangiectasia cases are summarized in Table 4.

Macroscopically, the lungs of all the ataxia-telangiectasia cases were consolidated with peripleural small vesicular emphysematous changes. Fibrinous exudative pleuritis was observed in cases 1 and 3. These patients had suffered a pneumothorax. The lungs were diffusely pale, and numerous 3–5 mm yellowish white nodules were noted throughout all lobes. Severe bronchiectatic changes were observed in cases 3 and 4. The lungs of case 3 showed honeycomb change in the lower lobes. Small sharp foci of bronchopneumonia were observed in all cases except case 1.

Microscopic examination revealed acute inflammation of bronchioles with apparent destruction by neutrophils and macrophages, and obliteration by the plugged fibrous and necrotic debris (Fig. 1). Organizing fibroblastic polyps extended from the side walls of respiratory and terminal bronchioles and obstructed respiratory bronchioles and the surrounding air space (Fig. 2). Some other bronchiolar structures were completely obliterated (Fig. 3). The adjacent pulmonary parenchyma was infiltrated by chronic inflammatory cells to differing degrees. Small numbers of lymphocytes infiltrated bronchioles with accompanying fibrosis and patchy organizing pneumonia. Plasma cells were rarely observed. Lesser numbers of lymphocytes infiltrated the alveolar wall. Cholesterol crystals surrounded by type II alveolar epithelial cells and foamy lipid were found in peribronchiolar regions. In subpleural lesions, small vesicular emphysematous changes were observed, especially in the lower lobes. In case 2, cytomegalovirus (CMV) inclusion bodies were observed in bronchiolar epithelium with accompanying desquamation and small areas of necrosis with haemorrhage (Fig. 4). In this case, CMV inclusions were mainly found in bronchiolar epithelium rather than alveolar epithelium. Some of the lumina of bronchioles were plugged with fibrous and necrotic debris, supporting the diagnosis of CMV necrotizing bronchiolitis. No true granulomas or giant cells were found in any case. Bacterial cultures of the autopsied lungs grew *Pseudomonas aeruginosa* in case 4. Viral cultures were not performed. All of the four cases were diagnosed histologically as bronchiolitis obliterans. The average number of affected bronchioles was 40% in case 1, 15% in case 2, 34% in case 3 and 28% in case 4. There was no difference between lobes in any case.

The features of pulmonary disease in the other five patients were two infections by *Pneumocystis carinii*, one patient with *Aspergillus* bronchitis and pneumonia, and two with bronchitis. Bronchiolitis obliterans was not found in these cases.

Immunohistochemical examination of case 1 revealed mycoplasma antigen in bronchial epithelium, in bronchiolar luminal exudate and the cytoplasm of exudative macrophages (Fig. 5a). Infiltrating lymphocytes were characterized as T-cells and B-cells in varying numbers without follicle formation. IgA producing plasma cells were rarely observed. Secretory component (SC), Lf and Lz localized in bronchiolar epithelial cells and submucosal macrophages, to the same extent as in control cases. Small numbers of T-cells (bearing UCHL-1 and CD3 antigens) were distributed in submucosal tissue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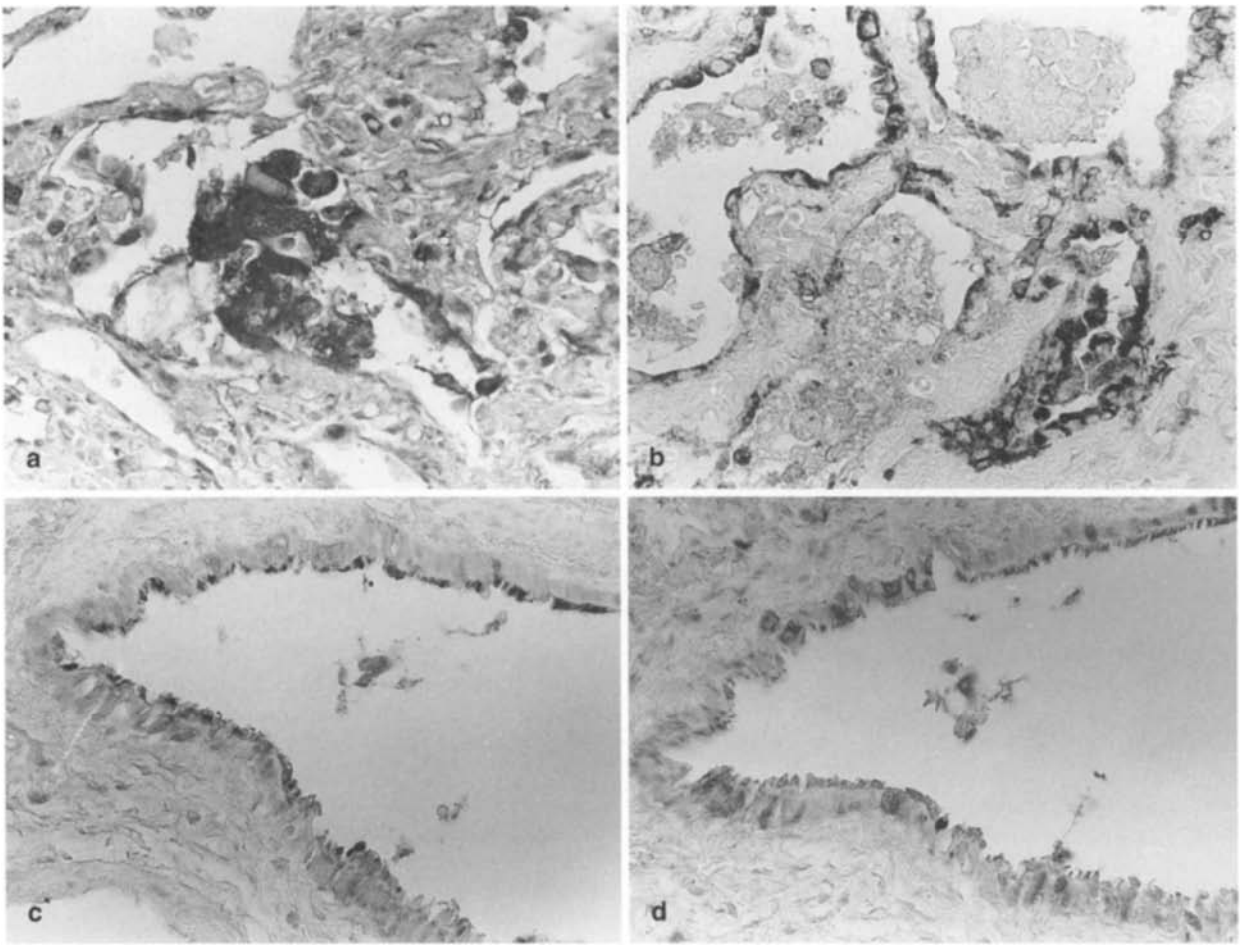

Fig. 5 **a** Indirect immunoperoxidase staining for mycoplasma antigen in case 1 showed positive staining in bronchiolar epithelium and exudative macrophages. Immunoperoxidase stains for HLA-DR(LN-3; **b**) antigen in case 1 showed strongly positive staining in bronchiolar and alveolar epithelium and alveolar macrophages. Staining for secretory component (**c**), lactoferrin (**d**) antigens showed positive staining in bronchiolar epithelium

◀ **Fig. 1** The wall of the terminal bronchiole has been replaced by an inflammatory reaction with neutrophils and macrophages. Necrotic tissue with leukocyte infiltration has plugged the terminal bronchiole. Remnants of the elastic tissue of the bronchiole are seen. (Case 3, Elastica-Masson stain)

Fig. 2 Fibrous polyp of organizing inflammatory reaction partially obliterates the terminal bronchiole. (Case 1, Elastica-Masson stain)

Fig. 3 The terminal bronchiole is completely obliterated by fibrous tissue with some lymphocyte infiltration. [Case 1, haematoxylin and eosin (H&E) stain]

Fig. 4 Early stages of obliterative bronchiolitis with CMV infection are characterized by acute inflammation and epithelial necrosis involving small bronchioles associated with an intraluminal inflammatory cell infiltrate. *Inset* depicts typical CMV inclusions. (Case 2, H&E stain)

with some infiltration of the epithelium. T-cell receptor (TCR) β bearing T-cells were relatively few in number compared with CD3 positive T-cells, especially within intraepithelial lesions. In all the ataxia-telangiectasia cases, the bronchiolar epithelium in bronchiolitis was HLA-DR positive as well as SC and Lf positive (Fig. 5b–d). No other evidence for the presence of anti-infectious agent antibodies was found.

Discussion

Ataxia-telangiectasia patients have functional and numerical T-cells defects and selective deficiencies of IgG2, IgG4, IgA and IgE, with increased concentrations of IgM [20]. IgA and mucosal defence peptides (such as SC, Lf and Lz) are important factors in mucosal defence. In this study, only small numbers of IgA producing plasma cells were observed in bronchiolar submucosal tissue in ataxia-telangiectasia patients. Although bronchiolar epithelium from the ataxia-telangiectasia patients expressed SC, Lf and Lz antigens, there were no significant differences in expression of these products relative to control cases. It has been reported that SC production in immunodeficient patients is normal or increased on the basis of immuohistochemical observations [18]. Recently the gene for ataxia-telangiectasia has been identified

and its product is similar to PI-3 kinase which mediates cellular responses to factors triggering cellular differentiation [24]. The immunodeficiency of ataxia-telangiectasia might be caused by a defect in a DNA recombination system involved in both repair of radiation damage and in the physiological rearrangement of immunoglobulin and T-cell receptor genes [10, 11]. Carbonari et al. [6] have reported an increased ratio of gamma/delta T-cells to alpha/beta T-cells in ataxia-telangiectasia. In our series of patients, immunodeficiency was characterized by hypogammaglobulinaemia, lymphopaenia and decreased T-cell responses to PHA stimulation in mixed lymphocyte culture. Recurrent episodes of respiratory tract infection occurred after a delay in the initial diagnosis of ataxia-telangiectasia.

Pulmonary disease in our ataxia-telangiectasia patients was characterized by bronchiolitis obliterans. Bronchiolitis and bronchiolitis obliterans are diseases of the small airways characterized by inflammation and obstruction of the bronchioles [12]. The frequency of bronchiolitis obliterans in infants and children is very low [21], and little is known about the epidemiology of this disorder. A review of primary immunodeficency disease other than ataxia-telangiectasia showed no case of bronchiolitis obliterans. We also reviewed age matched paediatric leukaemia cases at our institution, and bronchiolitis obliterans rarely occurs in these children (data not shown). Bronchiolitis obliterans has been ascribed to various aetiologies [16], including drugs, toxic fume exposure, allergic reactions, collagen vascular disease, organ transplantation, and proximal obstruction, as well as infections. In allogenic bone marrow transplantation (BMT), bronchiolitis obliterans is an almost uniformly fatal late complication of long-term BMT survivors [23], who develop chronic graft-versus-host disease [13]. The relative increase in T-cells with γ/δ receptors seen in ataxia-telangiectasia is similar to that observed in patients who have received allogenic BMT [28], and patients with HIV infection [7, 15]. In heart-lung transplantation, post-transplant bronchiolitis obliterans has emerged as the most important long-term complication [4].

Immunohistochemical studies of transplanted human lungs which have developed bronchiolitis obliterans have described induction of class II antigens on lung epithelial cells normally negative for these antigens such as those in bronchioles and alveoli [1, 26]. This study showed that normal lung epithelium was negative for MHC class II antigens (HLA-DR), but bronchiolar and alveolar epithelium consistently expressed HLA-DR in the lesions of bronchiolitis obliterans. Burke et al. [5] have hypothesized that bronchiolitis obliterans in heart-lung transplantation may arise from antigen deposition resulting in airway inflammation, with subsequent up-regulation of bronchial epithelium MHC class II expression, activation of recipient T-cells and a rejection reaction centred on the small airways. We speculate that in addition to MHC class II antigen expression on epithelial cells T-cells, and especially γ/δ receptor-bearing T-cells, are important in the immunopathogenesis of bronchiolitis obliterans. In this series, CD3 or UCHL-1 bearing T-cells were present in bronchiolar submucosal and intraepithelial tissue to the same extent as controls. TCR β bearing T-cells were relatively few compared to CD3 positive T-cells, especially within intraepithelial lesions. These findings suggest that bronchiolar intraepithelial T-cells bear non-— chain TCR. However, this must be confirmed by studies on fresh frozen material.

Katzenstein and Askin [16] describe a number of infectious aetiologies of bronchiolitis obliterans, implicating particular viruses, such as adenovirus and respiratory syncytial virus, as well as mycoplasma, and less often bacteria, fungi and mycobacteria. In our series, one case of mycoplasma infection was demonstrated by means of serology and immunohistochemistry. Bronchiolitis obliterans associated with *Mycoplasma pneumoniae* has been reported previously in a small number of cases [14, 22].

One case of ataxia-telangiectasia also demonstrated inclusion bodies characteristic of CMV infection in bronchiolar epithelium with necrotizing bronchiolitis. It has been reported that obstructive airway disease may be present in some HIV patients, and that CMV is a causative agent of necrotizing bronchiolitis [27]. *Pseudomonas aeruginosa* was cultured from lung tissue from one ataxia-telangiectasia patient. However, it was unclear whether this bacterium was pathogenic in this case. We could not demonstrate other infectious agents in these cases of bronchiolitis obliterans.

We have previously reported that paraquat administration induces expression of MHC class II antigens on bronchiolar and alveolar epithelium in an experimental rat model [19]. However, we did not find bronchiolitis obliterans in this model. In this study, expression of MHC class II antigens on bronchiolar epithelium was closely associated with the presence of bronchiolitis obliterans. We postulate that a pathological immunological event (especially T-cell dysfunction) is required for development of bronchiolitis obliterans as well as the expression of MHC class II antigens on bronchiolar epithelium.

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