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Comparison of the immunohistology of mucosa-associated lymphoid tissue in the larynx and lungs in cases of sudden infant death and controls

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Abstract The respiratory tract of children in the first two years of life, unlike that of adults, contains bronchus-associated lymphoid tissue (BALT) and larynx-associated lymphoid tissue (LALT) with no differences in frequency between SID and control children. Using immunohistochemical methods we examined the distribution of B, T, $CD4^+$ and $CD8^+$ lymphocytes, HLA-D^+ cells, $CD68^+$ macrophages and proliferating cells, comparing bronchus-associated and larynx-associated lymphoid tissue of sudden infant death cases and controls. In all groups the lymphoid tissue was organized in lymphoid follicles and parafollicular areas. With no differences in the cellular composition of BALT and LALT the lymphoid follicles contained mainly B lymphocytes with some $CD4^+$ lymphocytes in the germinal centers. Remarkably T lymphocytes of both subset types and B lymphocytes were observed in equal numbers in the parafollicular areas in contrast to gut-associated lymphoid tissue. However, the respiratory tract of young children with no differences between SID and controls might play a similar role in mucosal immunity and might function as an inductive site.

Key words Bronchus-associated lymphoid tissue (BALT) · Larynx-associated lymphoid tissue (LALT) · Respiratory mucosal immunity · Sudden infant death/syndrome (SID/S) · Young children

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Introduction

With respect to the etiology of sudden infant death (SID), respiratory infections have been discussed for many years (Althoff 1980). Mild infections of the respiratory tract, less commonly of the middle ear, gastrointestinal tract or other organs, were demonstrated by histological examinations in 30–85% of the cases (Wilske 1984; Entrup and Brinkmann 1990; Berry 1992). Therefore, an immune response in the respiratory tract might play an important role and be one possible trigger mechanism (Stoltenberg et al. 1992; Blackwell et al. 1993). A delayed or deficient immunological protection and a variable competence of cellular and humoral immunological reactions and an overstimulation of the mucosal immune system have been discussed as possible causative agents in cases of SID (Roche 1992; Reid and Tervit 1995; Stoltenberg et al. 1992, 1995).

An important part of the mucosal immune system consists of organized lymphoid structures called mucosa-associated lymphoid tissue (MALT), which is the site for antigen uptake and initiation of the mucosal immune response (Kraehenbuhl and Neutra 1992; Kato and Owen 1994). These functions are found in defined compartments with a typical subset composition of immunocompetent cells (Pabst 1987). In human adults MALT is found mainly along the gastrointestinal tract, e.g. Peyer's patches of the small intestine, and its cellular composition has been well studied (Spencer et al. 1985). In contrast to the gastrointestinal MALT, MALT in the larynx and lung of adults is only found under pathological conditions, e.g. in association with panbronchiolitis or cancer (Delahunty and Cherry 1969; Sato et al. 1992). However, in two recent studies of the respiratory tract of young children aged from 1 week up to 2 years, organized lymphoid structures showing the typical morphological signs of MALT were demonstrated in the lung and called bronchus-associated lymphoid tissue (BALT) (Tschernig et al. 1995) and in the mucosa of the epiglottis and Ventriculus laryngis, called larynx-associated lymphoid tissue (LALT) (Kracke et al. 1997). Both studies compared cases of sudden infant death (SID) and

children who had died from different traumatic and non-traumatic causes between 1986 and 1996. BALT was present in 40% of the children and LALT in 80% with no significant differences between the SID (n = 95) and the control group (n = 40). There was no correlation between respiratory infections and an increased frequency of BALT and LALT. The frequency of LALT did not change in the examined age group, in contrast to the probability of occurrence of BALT which increased significantly with the age of the children.

LALT and BALT, which together form the respiratory MALT of young children, might be part of the integrated mucosal immune system, but it is not known whether all lymphoid and accessory immune cells necessary to generate an immune response exist in these structures with the same composition/compartmentalization in sudden infant death and control children. LALT and BALT might therefore have the potential to initiate a mucosal immune response. In a recent study (Kracke et al. 1997) the distribution of B and T lymphocytes, ($CD4^+$ and $CD8^+$ T lymphocytes), in the larynx was examined immunohistologically for the first time. B lymphocytes and a few $CD4^+$ T lymphocytes were found in the lymphoid follicles of LALT, whereas in the parafollicular area B and T lymphocytes of both subset types were seen in equal numbers. The only available data concerning lymphocyte subsets of BALT in human fetuses and young children (15 victims of the sudden infant death syndrome and 2 infants who died from meningitis) was provided by Gould and Isaacson (1993). They mainly examined fetuses with infections and described unarranged aggregates of T and B lymphocytes in early gestation, which became more structured as gestation progressed. No distinction was made between fetuses with and without infections. This might be of importance because the occurrence of BALT in human fetuses is often associated with infections, which might influence the lymphocyte subset distribution in BALT. In BALT of young children these authors found the formation of germinal centres consisting of B cells surrounded by a loosely arranged mixture of B and T cells. However, they mainly examined SID children without comparing their findings to a control group. Although in other studies (Aoki 1994; Tschernig et al. 1995; Kracke et al. 1997) the frequency and morphology of respiratory MALT and respiratory infections (Kleemann et al. 1995) were not different between SID children and controls, SID children might not be necessarily representative of healthy young children in their cellular composition of MALT. Therefore, a comparison with children who had died from traumatic and non-traumatic causes is needed.

The aim of this study was to study the localization of the different lymphocyte subsets and accessory immune cells in the different compartments of BALT and LALT by immunohistochemistry. Furthermore the cellular composition of the organized lymphoid tissue between cases of SID and controls were compared to elucidate the role of respiratory MALT in SID.

Material and methods

Tissue collection and processing

As described in two previous studies (Tschernig et al. 1995; Kracke et al. 1997) lungs and larynges of young children with SID and different traumatic or non-traumatic causes have been examined for the occurrence of BALT and LALT. The tissue had been excised during medico-legal autopsies, performed in the Institute of Legal Medicine, Hannover Medical School, fixed in 4% buffered formaldehyde, dehydrated, embedded in paraffin and stained with hematoxylin eosin (H&E).

For this study tissue blocks of six lungs and five larynges from the previous studies showing organized lymphoid tissue in routine

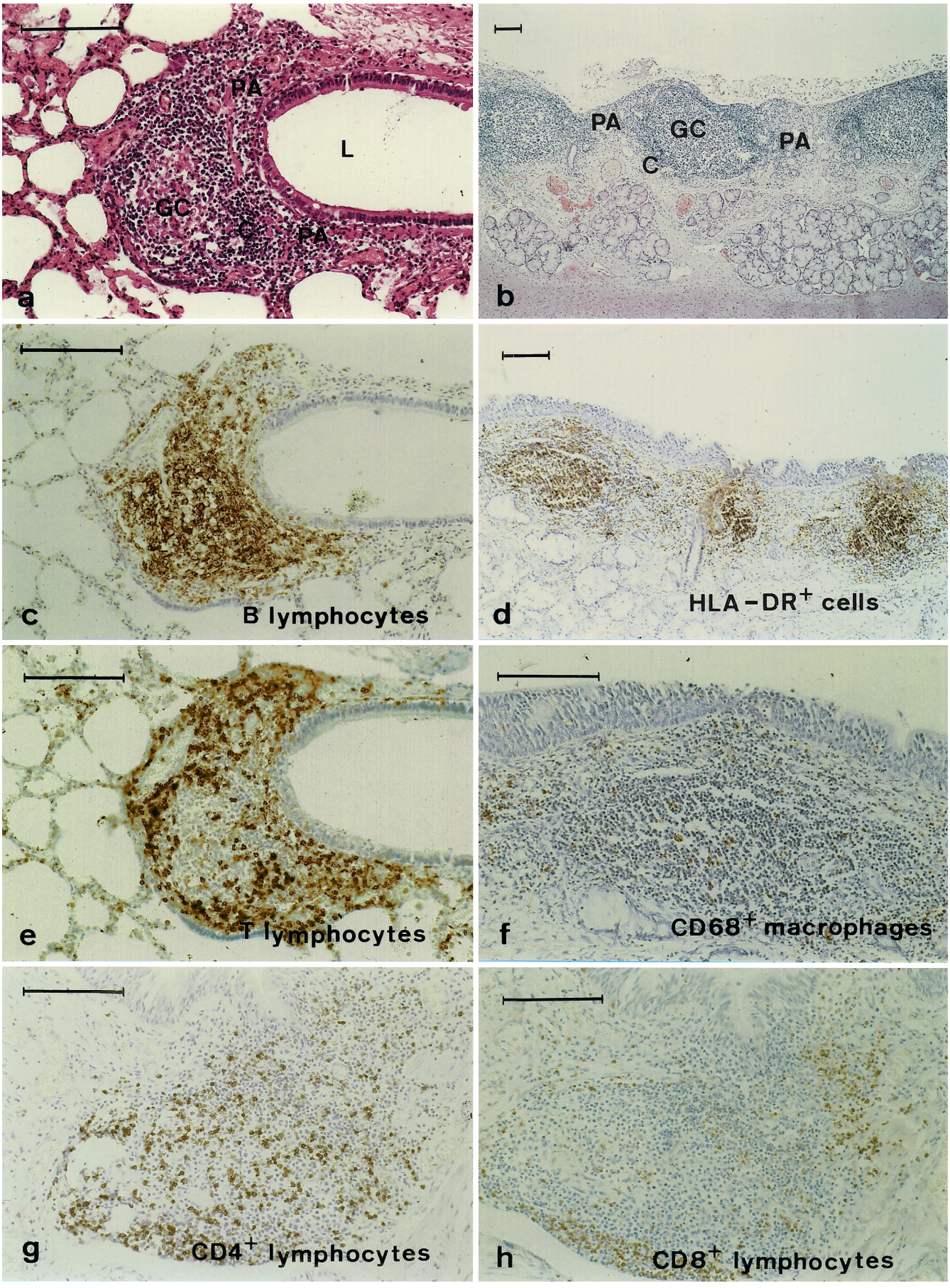
Table 1 Clinical data of the children

Laryngeal Tissue		
Age (days)	Sex	Cause of death
28	f	SID
80	m	SID
356	m	SID
255	f	Craniocerebral injury
268	f	Heart muscle inflammation and heart malformation
Lung tissue		
Age (days)	Sex	Cause of death
148	m	SID
253	f	SID
597	m	SID
278	m	Craniocerebral injury
445	f	Car accident
469	m	Drowning

SID: Sudden infant death

Table 2 Details of monoclonal mouse anti-human antibodies

Specificity	Monoclonal antibody	Dilution	Source/Reference
B lymphocytes (expect plasmacytoid differentiated cells and plasma cells)	L 26	1:50	Dako/(Ishii et al. 1984)
T lymphocytes	UCHL-1	1:180	Dako/(Smith et al. 1986)
$CD4^+$ lymphocytes	OPD 4	1:200	Dako/(Yoshino et al. 1989)
$CD8^+$ lymphocytes	C8/144B	1:10	Dako/(Mason et al. 1992)
$CD68^+$ macrophages	KP 1	1:200	Dako/(Pulford et al. 1989)
HLA-DR^+ cells	CR 3/43	1:50	Dako/(Smith et al. 1987)
Proliferating cells	Ki67	1:20	Dianova/(Key et al. 1993)


PA
L
GC
C
PA
a
PA
GC
C
PA
b
c
B lymphocytes
d
HLA-DR+ cells
e
T lymphocytes
f
CD68+ macrophages
g
CD4+ lymphocytes
h
CD8+ lymphocytes

◀ **Fig. 1 a–h** Bronchus- and larynx-associated lymphoid tissue (BALT and LALT) in young children: Morphology and distribution of lymphocyte subsets and accessory immune cells. **a**) Compartments of BALT: germinal centre (GC), corona (C) and parafollicular area (PA); bronchial lumen (L), H&E × 120 **b**) Compartments of LALT: germinal centre (GC), corona (C) and parafollicular area (PA), H&E × 30. **c, e, g, h**) Immunohistochemical staining of B, T, $CD4^+$ and $CD8^+$ lymphocytes, respectively in BALT, **a, c** and **e** are from parallel sections of the same BALT as are **g** and **h** × 120. **d, f**) Immunohistochemical staining of $CD68^+$ macrophages and HLA-DR^+ cells in LALT, d (60) and f(120) are parallel sections of the same LALT where f) is the lymphoid follicle seen in d). Each bar represents 100 μm

histology (BALT and LALT, respectively) were chosen (for clinical details of the children see Table 1). Using material of two different studies the comparison of LALT and BALT was not possible. Serial sagittal sections of the larynx including the epiglottis and serial sections of lung tissue were prepared and further processed for immunohistochemistry.

Immunohistochemistry

The serial paraffin sections of the larynx and lung tissue were mounted on slides coated with L-poly-lysin. After drying overnight, the sections were dewaxed and irradiated with microwaves in 0.01 M sodium citrate buffer (pH 6.0) for 25 min at 750 W. Consecutive sections were incubated for 60 min with one of the monoclonal antibodies listed in Table 2. Primary antibodies were detected with a commercially available ABC technique kit (Vecatastain Elite kit, Vector Laboratory, Burlingame, Calif.) according to the manufacturers' protocol. Negative controls omitted the primary antibody. All sections were counterstained with hematoxylin.

The distribution of lymphocyte subsets (B lymphocytes, $CD4^+$ and $CD8^+$ T lymphocytes), $CD68^+$ macrophages, HLA-DR^+ cells and proliferating cells in the organized lymphoid structures of the larynx and lung (LALT and BALT) was determined by light microscopy. The number of cells positive for the different markers were scored and compared for the different compartments of LALT and BALT.

Results

LALT and BALT were both organized in three different but not strictly separate compartments (Fig. 1a, b):

1. The germinal centre of the lymphoid follicle containing large cells with pale stained cytoplasma
2. The corona surrounding the germinal center consisting of small densely packed cells
3. The parafollicular areas.

In addition, immunocompetent cells were seen in the epithelium overlying LALT and BALT. A distinct dome area situated between the epithelium and the lymphoid follicle was not seen or was infinitely small in LALT and BALT of young children.

BALT

Between the SID and the control children with different traumatic and non-traumatic causes of death, no differences were seen regarding the compartmentalization or frequency of the immunocompetent and accessory cells examined. Thus, the following results are relevant for all groups.

Lymphoid follicle

In BALT typical secondary lymphoid follicles were found consisting of a corona and germinal centre. In the corona B lymphocytes but only a few T lymphocytes of the $CD4^+$ subtype were present, whereas in the germinal centre B lymphocytes and $CD4^+$ T lymphocytes were seen in almost equal numbers (Fig. 1c, e, g). These cells were loosely packed and some B cells had a blastoid appearance. Also in the germinal centre, a few proliferating cells positive for Ki 67 (not shown) were seen. Some large $CD68^+$ macrophages were found especially in the corona. Many cells stained positive for HLA-DR and these cells were evenly distributed over the lymphoid follicle.

Parafollicular area

In the parafollicular area T lymphocytes of both subsets ($CD4^+$ and $CD8^+$) and B lymphocytes were present (Fig. 1g, h). The number of B lymphocytes in the parafollicular area was as high as the number of T lymphocytes (Fig. 1c, e). No lymphocyte subset predominated in the neighbourhood of high endothelial venules (HEV). Some small $CD68^+$ macrophages were also seen in the parafollicular area, sometimes in close vicinity to the lymphoid follicle. Only a few proliferating cells were observed. Many cells stained positive for HLA-DR, but their number was not as high as over the lymphoid follicle itself.

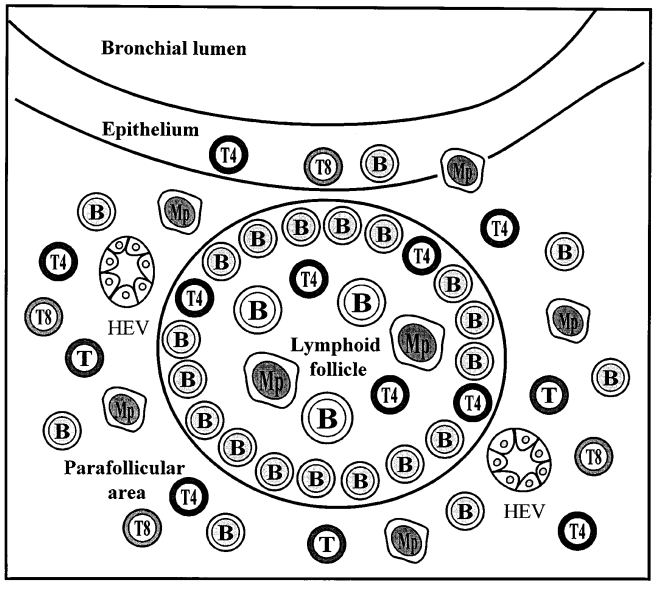


Fig. 2 Schematic representation of lymphocyte subsets and $CD68^+$ macrophages in BALT of young children. B: B lymphocytes; T: T lymphocytes; T4: $CD4^+$ lymphocytes; T8: $CD8^+$ lymphocytes; Mp: $CD68^+$ macrophages; HEV: high endothelial venules

Epithelium

In the epithelium overlying BALT B lymphocytes, $CD4^+$ and $CD8^+$ T lymphocytes and a few $CD68^+$ macrophages were seen infiltrating the epithelium, but overall the extent of infiltration was quite low. Positivity for HLA-DR was seen irregularly in the epithelium overlying BALT as well as in the rest of the bronchial tree epithelium.

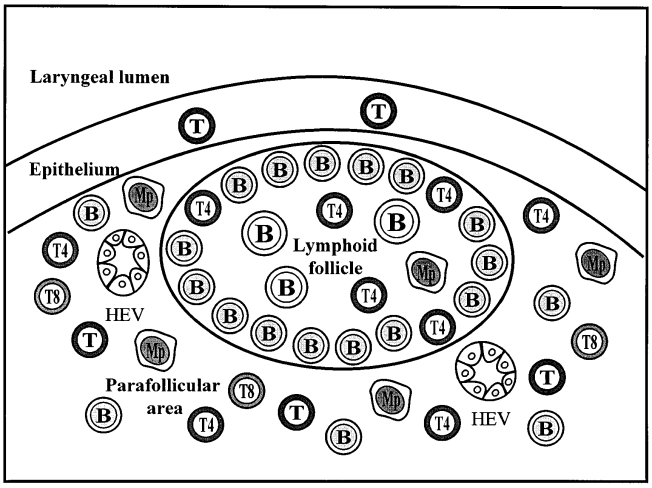


Fig. 3 Schematic representation of lymphocyte subsets and $CD68^+$ macrophages in LALT of young children. B: B lymphocytes; T: T lymphocytes; T4: $CD4^+$ lymphocytes; T8: $CD8^+$ lymphocytes; Mp: $CD68^+$ macrophages; HEV: high endothelial venules

LALT

The distribution of the examined immune cells also showed no differences in compartmentalization or frequency between SID and controls. The distribution of B and T lymphocytes and $CD4^+$ and $CD8^+$ cells in LALT, as described in a recent study (Kracke et al. in press), was similar to that in BALT.

Additionally, in the lymphoid follicle only a few small $CD68^+$ macrophages (Fig. 1f), some proliferating cells positive for Ki 67 especially in the germinal centre, and many cells positive for HLA-DR (Fig. 1d); in the parafollicular area some small $CD68^+$ macrophages, a few proliferating cells and many cells positive for HLA-DR; in the epithelium only a few proliferating cells (Fig. 1d, f) were detected.

In summary, the frequency and compartmentalization of the examined immune cells were quite similar in BALT and LALT. The distribution of lymphocyte subsets and macrophages in BALT and LALT is summarized in the schematic drawings (Figs. 2, 3). The amount of the cell types in the the different compartments of LALT and BALT is given semiquantitatively (Table 3).

Discussion

While it has been shown that BALT is not present in healthy human adults (Pabst and Gehrke 1990; Pabst 1992), no systematic studies are available for LALT. In young children from 1 week up to 2 years of age LALT and BALT are physiological components of the respira-

Table 3 Distribution of cells labelled by monoclonal antibodies in different compartments of LALT and BALT of young children

Lalt				
Cell type	Epithelium	Lymphoid follicle		Parafollicular area
		Corona	Germinal centre	
T lymphocytes	(+)	(+)	+	++
$CD4^+$ lymphocytes	–	(+)	+	(+)/+
$CD8^+$ lymphocytes	–	–	–	(+)
B lymphocytes	–	++	++	++
$CD68^+$ macrophages	–	(+)	(+)	+
$HLA\text{-}DR^+$ cells	–	++	++	+
Proliferating cells	+ (epithelial cells)	–	+	(+)
BALT				
Cell type	Epithelium	Lymphoid folicle		Parafollicular area
		Corona	Germinal centre	
T lymphocytes	(+)	(+)	+	++
$CD4^+$ lymphocytes	(+)	(+)	+	+
$CD8^+$ lymphocytes	(+)	–	–	(+)
B lymphocytes CD68	(+)	++	++	++
$CD68^+$ macrophages	(+)	+	(+)	+
$HLA\text{-}DR^+$ cells	–/(+)	++	++	+
Proliferating cells	–	–/(+)	+	(+)

– no positive cells were seen; (+) a few positive cells were present; + positive cells were present; ++ many positive cells were present

tory tract and are found in high frequency with no significant differences between SID and controls (Tschernig et al. 1995; Kracke et al. 1997). Recent studies suggested an increased Ig production in SID children compared to controls in tonsils and in the bronchial mucosa with differences in compartmentalization (Stoltenberg et al. 1992, 1995). It has been discussed that SID might be due to an overreaction of the mucosal immune system in a vulnerable phase of the immune system and the CNS which – via a common microbial factor – finally leads to coma and death (Stoltenberg et al. 1992; Gleeson et al. 1993; Rognum and Sangstad 1993). To understand the function of the respiratory MALT in SID and control children, a detailed knowledge of the composition of lymphocyte subsets and accessory immune cells in LALT and BALT is necessary.

This study was the first detailed comparative examination of the important immunocompetent cells in the respiratory MALT. Our data confirm that BALT and LALT of young children – with no differences in the distribution of immunocompetent cells between SID children and children who had died from different defined causes – consist of typical lymphoid follicles, which show a formation of germinal centres, contain mainly B lymphocytes and are surrounded by loosely arranged T and B lymphocytes (Gould and Isaacson 1993; Kracke et al. 1997). Thus, the results did not confirm a deficient or overreacting immune response in cases of sudden infant death, which is in accordance with recent studies (Lemke and Schäfer 1992; Bajanowski et al. 1997). Comparing the immune cells in BALT and LALT, there were only slight differences regarding the macrophages and the cells infiltrating the epithelium. In LALT the CD68 macrophages, especially in the lymphoid follicle, were rare and small whereas in BALT there were more numerous and larger. The epithelium cells covering LALT were not positive for HLA-DR, whereas in the epithelium overlying BALT positivity for HLA-DR was seen irregularly. The distribution of the lymphocyte subsets was similar in BALT and LALT, and thus the two types of respiratory MALT in young children may form a functional unit.

The distribution of lymphocyte subsets and accessory immune cells in human GALT has so far attracted much more attention than the respiratory tract MALT (MacDonald and Spencer 1994). At first glance the distribution of lymphocytes in LALT and BALT of young children seems to be the same as in human GALT (Spencer et al. 1985; Bjerke et al. 1993), however, there are differences in the cellular composition of the parafollicular area. Whereas in the parafollicular area of human GALT only a few B lymphocytes are present and the $CD4^+$ lymphocytes clearly outnumber $CD8^+$ lymphocytes, in the parafollicular area of LALT and BALT, B and T lymphocytes were observed in similar numbers and the $CD4^+$ lymphocytes seem to be only slightly more frequent than the $CD8^+$ lymphocytes. In fact, the lymphocyte subset composition in the parafollicular area of the respiratory MALT resembles that of the dome area of human GALT, which lies between the epithelium and the lymphoid follicle (Pabst 1987). Furthermore, in the parafollicular area of the respiratory MALT many $HLA\text{-}DR^+$ cells and a few $CD68^+$ macrophages were found, which is also characteristic of the dome area in human GALT (Brandtzaeg and Bjerke 1989; Bjerke et al. 1993).

In conclusion, in LALT and BALT of SID cases and controls with traumatic and natural causes of death, all lymphocyte subsets and accessory cells necessary to initiate a mucosal immune response are present, and the distribution of these cells is comparable to the distribution of immunocompetent cells in the dome areas and lymphoid follicles of human GALT. However, a clear-cut T-cell zone, such as the parafollicular compartment of GALT, is missing in the respiratory MALT of young children. It is generally believed that GALT mainly initiates mucosal immune responses in the gastrointestinal tract (Brandtzaeg 1995; Kraehenbuhl and Neutra 1992). With respect to the similarities in cellular composition one might draw the conclusion that the respiratory MALT functions in a similar way to GALT, and therefore might be the inducer of respiratory mucosal immune responses in young children. However, the functional implications of the missing T-cell zone in LALT and BALT of young children need to be studied further.

It is now clear that LALT and BALT possess the cellular basis to initiate a mucosal immune response, but to prove that they really function as an inducer of respiratory mucosal immunity in young children two major questions must be answered:

1. Are antigens from the lumen transported through the epithelium overlying LALT and BALT to the underlying lymphoid tissue?
2. Are antigen-specific cells generated in LALT and BALT after being challenged with antigens?

These questions will be difficult to answer in humans. In BALT of rats antigen uptake and antigen-specific cells have been demonstrated after challenge with antigen (Morin et al. 1994). There have been no functional studies on LALT in experimental animals. It must also be kept in mind that the function of BALT in experimental animals does not necessarily reflect the situation in humans, because the structure occurrence and function of BALT, and probably LALT, vary widely between species and age groups (Pabst and Gehrke 1990).

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