Bronchus-associated lymphoid tissue (BALT) in the lungs of children who had died from sudden infant death syndrome and other causes

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Abstract

Background – Bronchus-associated lymphoid tissue (BALT) is well characterised in rabbits and rats. In humans, however, it does not seem to be present in the healthy adult lung, although it can develop after certain microbial stimulation.

Methods – In the present study a consecutive series of lungs from 88 children who had died of sudden infant death syndrome (SIDS) and 34 control cases of comparable age were examined for the presence of BALT.

Results – BALT was present in 36.4% of the patients who had died of SIDS and in 44.1% of the control cases. The probability of finding BALT increased with age, with similar kinetics in both groups.

Conclusions – Future studies need to define when and at what rate BALT disappears as children get older. In young children BALT may act as an entry site for antigens to initiate an immune response, as is well documented for the gut-associated lymphoid system.

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Keywords: BALT, SIDS, normal lung.

Figure 1 BALT at a bifurcation of the bronchi in a lung of a child who died of SIDS: (A) overview; (B) higher magnification (bar = 200 μ m).

Twenty years ago Bienenstock *et al*^{1,2} introduced the term “bronchus-associated lymphoid tissue” (BALT) as an analogue to the well defined “gut-associated lymphoid tissue” (GALT), the best known example of which are Peyer’s patches. Also around this time Emery and Dinsdale^{3,4} published data on the frequency of lymphoid aggregates in children. Typical BALT consists of a follicle-like accumulation of lymphoid cells infiltrating the bronchial epithelium. In some species these are specialised epithelial cells (the M cells) which, in Peyer’s patches, are the entry sites for particles, bacteria, and viruses.⁵ The available data suggest that BALT plays a central part in lung immunology – for example, in antigen sampling, presentation and initiation of immune responses to aerogenic antigens.⁶ The organisation of lymphocyte subsets, dendritic cells, and the vascular system is much more complex in BALT than in Peyer’s patches, and varies between species.⁷ There is also great variability in the frequency with which BALT occurs in different species, and BALT has not been found in humans without a history of lung infection.^{8,9} In recent reviews the role of BALT in respiratory tract immunity in healthy humans has been reconsidered.^{5,10,11} BALT-like structures have been reported in patients with various pulmonary infections.⁵ The difference between normal and diseased lungs has resulted in several detailed studies of the number and size of BALT in human lungs under different pathological conditions. BALT was found in smokers, but without M cells,^{12,13} and in fetal and infant lungs it was invariably associated with infections.¹⁴ BALT was found in 12 of 17 patients with diffuse panbronchiolitis, similar to findings in animals.¹⁵ In 100 lung specimens with the diagnosis “inflammation” the frequency of BALT was 8%.¹⁶ These findings led

Figure 2 BALT in a lung of a child who died of lethal trauma: (A) overview; (B) higher magnification (bar = 200 μ m).

to a recent editorial questioning whether it is part of the normal host defence mechanism or whether it is useful as an entry site to immunise the common mucosal immune system and thus be of therapeutic value.¹⁷

As a result of the increasing interest in the underlying mechanisms for the generation of BALT in humans, its incidence in the lungs of children who had died from sudden infant death syndrome (SIDS) was studied. Furthermore, since some of the differences in the lymphoid system are age-dependent – for example, large adenoids in children but hardly any lymphoid tissue in adults – it was important to elucidate whether BALT is absent from the lungs of healthy children, as is the case in adults.

Methods

Histological sections of the lungs of 88 children who had died from SIDS and 34 children who had died from congenital malformation, known severe diseases (natural death) or lethal trauma (including accidents and child abuse) were studied. All consecutive cases recorded in the

Department of Legal Medicine from 1988 to 1990 were divided into the two groups. SIDS was defined (according to Beckwith¹⁸) as “sudden death in any infant or young child between seven and 730 days which is unexpected by history, and in which a thorough post mortem examination fails to demonstrate an adequate cause of death”. Mild infections of the upper respiratory tract or middle ear were not considered to have been the cause of death.

In 73 cases of SIDS and 30 control cases haematoxylin and eosin-stained sections of a central and peripheral part of the lung were available. These were used for calculating the probability of the presence of BALT at a certain age. Lymphoid aggregates in the interstitium in an unusual perivascular location or near to bronchial glands were not considered to be BALT, but only those lymphoid aggregates associated with the bronchi and infiltrating the muscularis mucosae and the epithelium.

The presence of BALT was noted per section and the size of the whole section determined. The probability of the presence of BALT as a function of age was calculated from the estimates of a logistic regression (BMDP package) with $p < 0.01$ being considered significant.

Results

In the control group there were as many girls as boys, but in the group with SIDS the ratio of boys to girls was 2:1. The mean (SD) of the area of the sections of lung evaluated was 1.3 (0.5) cm². The frequency, size, and structure of BALT in the different control groups were similar so the results obtained from the lungs of children who had died from natural causes or lethal trauma were pooled. Although the lung tissue was preserved to a variable degree, and oedema and congestion was found in several specimens, the clear identification of BALT was not impeded by these factors.

CONTROL LUNGS

BALT was found in 15 (44.1%) of the 34 control cases. The size of the BALT was variable and it consisted of follicle-like aggregations (fig 1A) with some venules and a cuboidal epithelium at different sites which infiltrated the epithelium to a variable degree (fig 1B).

LUNGS FROM CHILDREN WITH SIDS

In the SIDS group BALT was found in the lungs of 32 (36.4%) of the 88 cases, and the structure was comparable with that in the lungs of the control group (fig 2A,B). When the ages of the children of both groups were plotted against the probability of the presence of BALT (fig 3), the probability was higher in the SIDS group at any age studied but this difference was not statistically significant. The influence of age on the probability of the presence of BALT was significant ($p < 0.01$), both groups showing a parallel increase in probability with age. Furthermore, the control cases were distributed evenly over the whole age period studied, but the children with SIDS were pre-

Figure 3 Probability of the presence of BALT in lung sections of children who died of SIDS or other causes depending on age. The probability was calculated from the estimates of a logistic regression in 73 children who died of SIDS and 30 who died from other causes. The youngest patient with SIDS was nine days old and the youngest child in the control group was seven days old. No significant difference was seen between patients with SIDS and the controls, but the influence of age was significant ($p < 0.01$).

dominantly found in the age span up to 300 days (fig 3).

Discussion

This study confirms that BALT is found in the normal lungs of children in a frequency which significantly increases with age. This is in contrast to findings in the lungs of adults.⁸ In children who died of SIDS, however, the frequency of the presence of BALT was not significantly different. The frequency with which BALT occurs in the lungs of children might even be higher than in the present study, as sections from only two areas were screened. Emery and Dinsdale³ also described an increasing frequency of lymphoid aggregates in children with age, while these aggregates were only seen in two of 50 lungs of stillborn babies. The same authors⁴ found a tendency to a higher number of BALT in the lungs of children with SIDS than in the present study. This difference might be explained by the fact that all lungs showing any disease – for example, mild tracheitis, bronchitis or other inflammatory reactions – were excluded,⁴ whereas in the present study all sections of consecutive cases were evaluated.

The following hypothesis on the development of the function of BALT in the human lung should be tested in future studies. (1) There is no BALT in the lung at birth, which differs from other lymphoid tissues such as tonsils, lymph nodes, Peyer's patches, etc. (2) In the first few months of life inhaled antigens (probably of microbial origin) stimulate the development of BALT. (3) After contact with most environmental antigens BALT is no longer necessary, and the dendritic cells in the bronchial epithelium take over the role of antigen uptake and presentation.¹⁹ (4) In the adult chronic stimuli or specific bacteria induce

the reappearance of BALT – for example, in smokers^{10,11} and patients with post-stenotic inflammation.¹⁴ (5) A further unknown stimulus can induce a malignant transformation leading to the development of tumours of BALT, or BALTomas.²⁰

Holt²¹ has recently argued that the differences between the responses to food and inhaled antigens and the development of atopy might be due to an organ-specific age pattern of the presentation of antigen in early childhood. BALT might have a role here too.

Future studies should investigate which stimuli cause the development of BALT in young children and whether its disappearance coincides with the appearance of dendritic cells in the bronchial epithelium. Furthermore, antigen uptake by BALT should be studied in the same detail as in Peyer's patches using an adequate animal model.

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