Peripheral inflammation is more important than central inflammation

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Direct evidence supporting a pathophysiological role for the peripheral airways in asthma has come from studies, where central and peripheral pulmonary resistance were compared (1). During both the inspiration and expiration phases, peripheral resistance was significantly increased in asthma patients compared with normal individuals, and this was particularly evident in patients with moderate to severe disease.

Inflammatory Changes in the Small Airways

Evidence of inflammatory changes in the small airways has been obtained from microscopic analysis of post-mortem samples, which show constriction, thickening, and cellular infiltration of the airway wall. This technique has a number of disadvantages: the bias towards samples from severe cases and possible effects of systemic steroid therapy, and the difficulty of differentiating changes resulting from the disease process from those associated with either tissue preservation or caused by death. Immunocytochemical staining and molecular biological techniques have been found unsatisfactory on such material.

The alternative technique, that of endoscopic biopsy also has disadvantages. It may be unrepresentative of the region or airway as a whole, since only a very small piece can be sampled, and specimens obtained exclude tissue from beyond the smooth muscle.

Some of the limitations of the above techniques have been overcome by the use of frozen, surgically-resected lung, but material is available only from a limited number of patients. Samples of this type have allowed the airway to be examined systematically, with sequential samples being taken from airways ranging in diameter from 18 mm to < 2 mm. Studies of inflammatory markers in such samples have indicated that in asthma patients, compared with those without asthma, there is a similar increase in T-cell number and total eosinophil numbers, and that this occurs in both large (>2 mm) and small (<2 mm) airways (2). Mast cell numbers have been found to change only in small airways. An inverse correlation between the size of the airway and the accumulation of T-cells and eosinophils has been observed. The presence of greater numbers of eosinophils around small airways compared to large airways and in the parenchyma has been confirmed by immunocytochemical staining (2).

Inflammatory events in the tissues immediately either the side of the smooth muscle layer have also been evaluated using the same marker identification techniques. This indicated a similar accumulation and distribution of T-cells in the two sites, but a greater number of resting eosinophils were found outside the smooth muscle layer, even in patients with mild asthma (2). Conversely, an increased concentration of activated (EG2+) eosinophils were identified in tissue internal to the muscle layer. There is now evidence that smooth muscle may actively participate in the recruitment of inflammatory cells by production of chemokines, such as eotaxin, MCP-4 and RANTES (3,4). Although some expression of eotaxin was noted in normal individuals, much higher levels were found in asthma patients and occurred in both large and small airways, providing further evidence that both areas of the lung may participate in eosinophil recruitment.

Tissues examined for evidence of the major inflammatory cytokines implicated in asthma, specifically interleukin 4 (IL-4) and IL-5, indicated that the number of cells expressing mRNA for each cytokine
was increased in asthma patients relative to controls (5), but with interesting differences. IL-5 mRNA expression was greater in the small airways compared to the large airways, while the situation was reversed for IL-4 mRNA.

References


4. Hamid Q.A. Unpublished observations