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Localization of IgE to lung germinal lymphoid follicles in a patient with allergic bronchopulmonary aspergillosis

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Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease of the lung caused by sensitivity to the ubiquitous organism *Aspergillus fumigatus* (Af).¹ The uniform presence in ABPA of positive immediate skin test reactions to *Aspergillus*, markedly elevated serum total IgE levels, and a marked increase in IgE anti-*Aspergillus* (IgE-Af) speak for the importance of IgE to *Aspergillus* in the diagnosis of ABPA.¹ Until now, only indirect evidence existed of IgE production in the lungs of patients with ABPA.² In this report we present evidence obtained from examination of a lung biopsy from a patient with ABPA of localization of IgE in the germinal lymphoid follicles of a lung with ABPA.

CASE REPORT

A 13-year-old boy was evaluated for persistent pulmonary infiltrates. Atopic dermatitis developed in him at age 18 months. At age 12 years a cough developed associated with left-sided pulmonary infiltrate and partial atelectasis found on chest radiography. Ten days of erythromycin resulted in symptomatic improvement but no change in chest radiog-

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
IgE-Af:	IgE anti- <i>Aspergillus</i>
BAL:	Bronchoalveolar lavage
IgA-Af:	IgA anti- <i>Aspergillus</i>
H & E:	Hematoxylin and eosin
MBP:	Major basic protein

raphy findings. Bronchoscopy results were normal. One month later the pulmonary infiltrate increased. At this time the patient also had night sweats, headache, and a low-grade fever. Bronchoscopy on this occasion revealed purulent exudate from the lingula, with granular fragments. One month later thoracotomy with resection of the left lingular segment was performed. Our evaluation at this time revealed a strong positive *Aspergillus* skin test, positive serum precipitins to *Aspergillus*, peripheral blood eosinophilia of 13%, and a total serum IgE of 5500 IU/ml. The patient was started on oral prednisone, with resultant marked clinical improvement.

MATERIAL AND METHODS

Immunofluorescent staining

Indirect immunofluorescence was used to detect both the localization of IgE and the presence of eosinophil granule major basic protein (MBP) as previously described.³⁻⁶

RESULTS

By light microscopy, an intense inflammatory infiltrate was observed in the lung parenchyma. The

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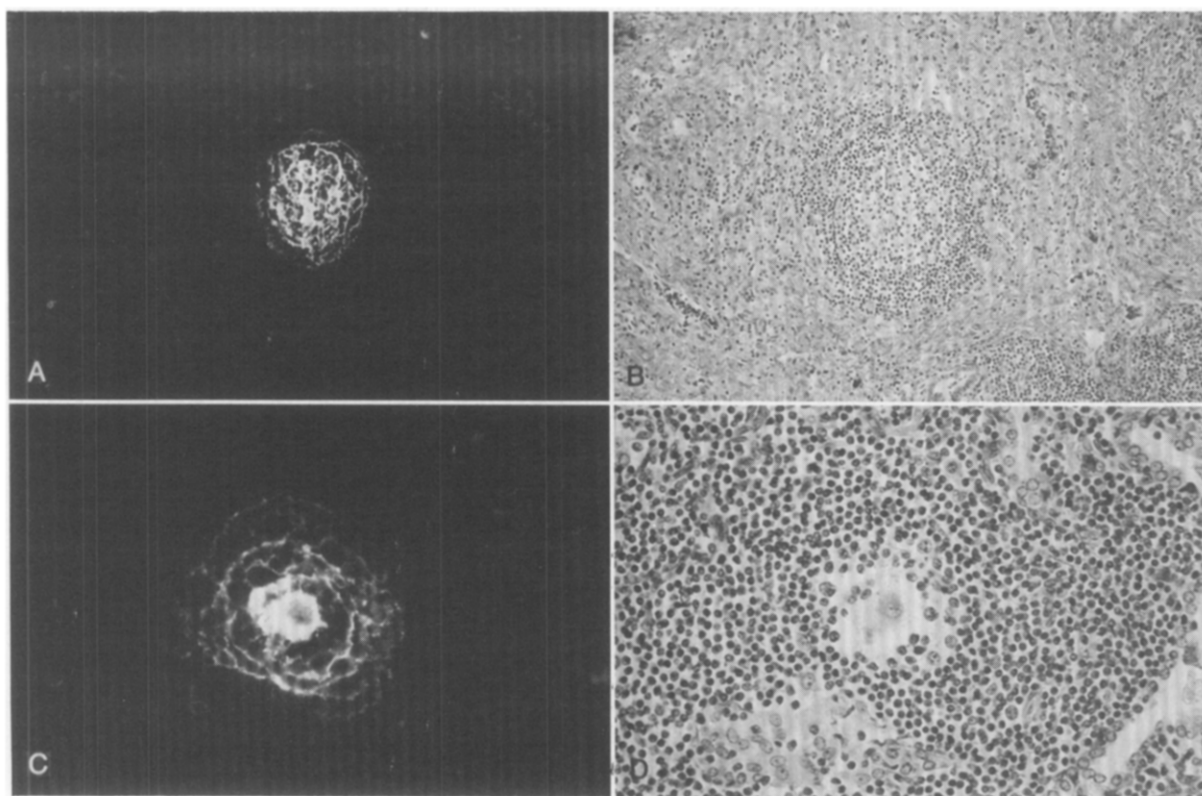


FIG. 1. Immunofluorescent localization of IgE in lung tissue removed surgically from a patient with ABPA. **A** and **C**, sections stained with affinity-purified rabbit antihuman IgE. **B** and **D**, the same sections as in **A** and **C**, counterstained with H & E. In **A**, note marked staining for IgE within the germinal center of a secondary follicle. At higher magnification (**C**), intense staining for IgE is also present in the germinal center of another secondary follicle. Note that the staining pattern for IgE appears to outline cell margins, suggesting either the presence of membrane-bound IgE or peripheral cytoplasmic localization of IgE. In **D**, the cell in the center containing the greatest staining for IgE is likely a macrophage. A serial section stained with protein-A-purified NRlgG was negative (results not shown). (**A** and **B**, original magnification $\times 160$; **C** and **D**, original magnification $\times 400$.)

immunofluorescence staining with anti-IgE showed striking localization of IgE to germinal centers sitting in the midst of secondary follicles (Fig. 1). Nine secondary follicles with germinal centers were identified by examination of the hematoxylin and eosin (H & E) counterstained section; all nine demonstrated IgE staining by immunofluorescence. In the section stained with anti-MBP, numerous eosinophils and extracellular MBP deposition were observed in the mucus in the bronchial lumen as we have previously noted.⁷

DISCUSSION

Many aspects of the disease process of ABPA strongly suggest the critical contribution of IgE. In addition, animal model investigations have verified the necessity of both IgE and IgG anti-*Aspergillus* antibodies in the pathogenesis of the disease.^{8,9} To date, the only implication that IgE is produced locally

in the lung of ABPA comes from one study comparing IgE anti-*Af* levels in bronchoalveolar lavage (BAL) fluids and sera. BAL was performed in eight patients with ABPA when their chest x-ray films were normal and respiratory status stable.² The ratios of anti-*Af* antibodies in BAL fluids compared with sera (both expressed as anti-*Af* antibody/albumin) in patients with ABPA were 48 for IgE, 96 for IgA, and 0.94 for IgG, suggesting local production of IgE and IgA but not IgG antibodies to *Af* in the bronchoalveolar compartment. However, the ratio of BAL total IgE/albumin divided by total serum IgE/albumin was 0.93, suggesting that in these patients the bronchoalveolar compartment is not the source of the significant elevation in total serum IgE in ABPA. These findings are consistent with a prior study of IgE in nasal secretions in which the nasal fluid IgE/total protein ratios were less than those in serum.¹⁰ Nonetheless, the analysis of specific IgE suggested that IgE was present

in nasal washings in higher concentrations than expected on the basis of simple diffusion. These differences in ratio of specific-to-total IgE were considered evidence for a model in which IgE is produced locally but predominantly diffuses into serum.¹⁰ Our findings showing the presence of IgE localized in the germinal centers of ABPA lung support the concept of local IgE production.

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Rhinitis and asthma caused by occupational exposure to carob bean flour

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Vegetable gums, such as acacia, tragacanth, and guar, are known causes of occupational rhinitis and asthma. Carob bean flour is another substance derived from a vegetable that grows in the Mediterranean region. It has been used industrially since the beginning of the twentieth century as a thickening agent in food products (ice cream, margarine, preserved foods, pet foods), and it is used in infant feeding for the control of diarrhea and vomiting.¹

CASE REPORT

The patient was a 48-year-old man who had been employed for 16 years in a jam factory. After 2 years in his

job, he complained of work-related rhinitis and irritated eyes; asthma appeared 3 years later. Rhinitis occurred during his work, and he had asthma during the night after work; symptoms disappeared on weekends or on holidays. During the last years, asthma tended to become more chronic. His job consisted of handling thickeners and hardeners in dry form (powder): carob bean flour (Idealgum; Idea, Milano, Italy); a blend of guar gum, carob bean flour, and carrageenan (Frimulsion N 40, Cesalpinia, Bergame, Italy); and pectin (Genu, Copenhagen, Denmark). He had no personal or familial history of atopy. IgE level was 31 IU/ml; lung function testing showed an obstructive syndrome (forced expiratory volume in one second [FEV₁] 68%, forced vital capacity [FVC] 93%, total lung capacity [TLC] 95% of predicted), with a baseline peak expiratory flow rate (PEFR) value of 500 L/min. Skin prick tests were performed with Idealgum 1/1000, Frimulsion N 40 1/1000, Genu 1/1000, and pure guar gum 1/1000 (Viscogum 3000A, Sanofi Bio-Industrie, Brussels, Belgium), diluted in phosphate-buffered saline. All were negative. Skin prick tests were also negative in five control subjects. A single-blind provocation test was performed (manipulation of carob bean flour for 15 minutes)

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