Hypersensitivity Bronchopulmonary Aspergillosis*

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Seven patients with recurrent pulmonary densities, peripheral blood eosinophilia, purulent sputum with the fungus Aspergillus fumigatus and precipitating antibodies to extracts of this fungus were found to also have dual phase skin tests. These were characterized by an immediate component, reagin mediated, and a second phase, precipitin mediated, appearing three to six hours later. Biopsies of this latter phase showed perivascular infiltration with eosinophils, and deposition of IgG and B, C, by immunofluorescence microscopy techniques. The patients varied in stages of illness. One had her first episode after a long history of recurrent asthma, several had recurring episodes with one going on to develop a pulmonary mucus plug, and one presented with a mucus plug. Adrenal corticosteroids were used with excellent results, and are recommended for therapy.

In 1952 Hinson et al1 described a syndrome of recurrent pyrexial attacks, changing radiologic patterns of pulmonary infiltration, purulent sputum containing the fungus Aspergillus fumigatus and a peripheral blood eosinophilia. Since that time dual-type skin test reactions,2 immediate wheal and flare followed in several hours by erythema and induration, and precipitating antibodies to this fungus have been demonstrated in association with this syndrome.3,4 Prior to this description, Craven,5 in 1935, described four cases of similar nature from his practice in the southern United States of America. Most of the cases discussed in the English language literature have emanated from Great Britain,6,7 but there have been a few isolated North American reports alluding to this syndrome.6-13 This report and review summarizes seven cases which have been seen during 1967 at The Royal Victoria Hospital (Montreal, Canada). In some of the patients the syndrome was in an active phase, while in others the diagnoses were made in relative retrospect, with all definitive skin and precipitin tests being performed during 1967.

CASE REPORTS

Recurrent purulent sputum associated with febrile episodes, chills, weight loss of varying degrees and asthmatic breathing were reported by most of the patients in the group. A background of bronchitis, asthma or other atopic disease was also found. On examination during exacerbations all patients were found to show evidence of weight loss, prolonged expiratory phase of respiration with diffusely scattered rhonchi and rales localized to areas shown to have densities by radiography. These x-ray shadows represented a spectrum of pulmonary densities, as shown in Figures 1 to 3. The diagnosis was made for one patient, M. H., during her first episode of infiltration after a long history of asthma. Patients L. L., H. M., S. S., and R. O., had recurrent pulmonary densities demonstrated over a period of years, with the segmental shadows waxing and waning, often recurring in previously involved areas and usually leaving increased lung markings upon clearing. N. S. had recurring infiltrates but developed a mucus plug syndrome after several years of illness, and R. M. presented initially with a segmental collapse in the right upper lobe, also interpreted as a mucus plug syndrome. He had had minor episodes of recurrent bronchitis without documented evidence of infiltrations and developed asthma after the mucus plug was demonstrated. Bronchography performed on several of the patients showed evidence of bronchiectasis. Figure 4 demonstrates the results of one such examination, with the secular proximal dilatations and normal distal filling of the bronchial tree. This area had previously been involved with infiltrations on several occasions.

As shown in the Table, except for R. M., all patients had a significant peripheral blood eosinophilia, precipitins against A fumigatus demonstrated in their serum by double diffusion in agar gel (Fig 5), sputum eosinophilia...
and a positive culture of *A. fumigatus*. Two patients had on several occasions coughed up plugs.

The results of other laboratory investigations for parasites, L.E. cells, antinuclear factor, rheumatoid factor and C-reactive protein were negative. Renal and liver profiles were normal. Serum protein electrophoreses revealed decreased albumin, elevated α₂-globulin and normal γ-globulins. Immunoglobulin quantitation showed elevated IgA and IgM levels on one occasion in one patient.

Skin tests showed a dual response to extracts of *A. fumigatus* in all patients except M. H. who was tested while she was receiving corticosteroids. She showed a positive immediate response; however, several years previously she had had a severe reaction characterized by swelling of the arm and asthma, which developed about 12 hours after a series of skin tests including that for *A. fumigatus*. Biopsy of one dual reaction, at 24 hours, showed perivascular infiltration with eosinophils and polymorphonuclear leukocytes as well as edema. Immunofluorescence microscopy with antI IgG, B₁C. and IgM showed localization of IgG and B₁C. in the walls of vessels from the center of the reaction (Fig 6–8).

Tests with other common allergens were often positive when performed; however, skin tests in search of other fungal diseases were negative. Old tuberculin (OT) 1/1,000 was negative in all cases but at 1/100 was positive in several instances.

The clinical course was similar in all except R. M. With conventional antibiotic and bronchodilator therapy little progress was made, but there was a dramatic response on the administration of corticosteroids with the peripheral eosinophil counts, pulmonary shadows, increased airways resistance and slightly lowered diffusing capacity returning towards normal as shown by serial studies. Upon withdrawal of therapy in several instances the syndrome recurred, but subsequently responded on resumption of corticosteroid therapy. An attempt to hyposensitize N. S. during a period off corticosteroids resulted in repeated episodes of increasing asthma and swollen painful arms which developed six to eight hours after each injection. M. R. and N. S. have received aerosolized acetylcysteine (Mucomist®)

**Figures 1 and 2.** N.S., segmental involvement on two occasions.

**Figure 3.** N.S., right middle lobe mucous plug, and residual reticular pattern in both upper lobe areas.
HYPERSENSITIVITY BRONCHOPULMONARY ASPERGILLOSIS

and nystatin (Mycostatin) in an attempt to dissolve the plugs. The results of this regimen seemed favorable with eventual expectoration of the large plugs.

**DISCUSSION**

Hinson's patients\(^1\) had similar histories of transient febrile episodes extending over months or years with varying symptom-free periods between them. Severe cough and purulent sputum with occasional blood tingeing were associated, as was asthma to some degree. During acute episodes there was dyspnea and often a vague discomfort in the chest. Each of these features was seen in all the cases outlined above, with the exception of patient R. M., which resembled Hinson's case V and somewhat those of Sanerkin et al.\(^1\) In this case, there was no documentation of febrile episodes, although the patient did complain of cough, at times more severe, productive of transiently purulent sputum, and episodes of asthma.

Examination of the sputum produced during the acute episode is of great clinical significance. It is always purulent looking, and a particularly important feature is the presence of the mycelium in white or brownish flecks just visible to the naked eye. On occasion, these mycelial flecks have been aggregated together with Charcot-Leyden crystals, Curschmann spirals, mucus, eosinophils, and pus cells into firm, rounded, granular, dull brownish masses measuring up to 1 cm in diameter and termed "plugs." Patients R. O. and N. S. described such expectorated masses, but no examination was carried out at the time. The eosinophils, spirals and crystals may be found in the sputum generally, not only in the plugs, and between episodes the fungus may be seen only intermittently. All of the above patients have displayed *A fumigatus* in the sputum, and most have shown sputum eosinophilia at some time during attacks.

**Table 1—Background and Some Laboratory Examinations on the Seven Patients.**

<table>
<thead>
<tr>
<th>Sex, Age</th>
<th>Background</th>
<th>WBC Eosinophils</th>
<th>Skin Tests</th>
<th>Other Allergens</th>
<th>Preputial</th>
<th>Sputum</th>
<th>Culture</th>
<th>Plug</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.H. F, 43</td>
<td>Urticaria, childhood asthma</td>
<td>7,100 21,300</td>
<td>Dual reaction</td>
<td>Several positive</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
<tr>
<td>L.L F, 45</td>
<td>Recurrent bronchitis, wheezing, chills</td>
<td>7,700 8,100</td>
<td>Dual reaction</td>
<td>Not done</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
<tr>
<td>S.S. F, 48</td>
<td>Teen-age eczema, sinusitis</td>
<td>6,000 15,800</td>
<td>Dual reaction</td>
<td>Several positive</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
<tr>
<td>R.O. M, 32</td>
<td>No symptoms</td>
<td>7,000 12,000</td>
<td>Dual reaction</td>
<td>Several positive</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
<tr>
<td>R.M. M, 62</td>
<td>Chronic cough, heavy smoking</td>
<td>8,000</td>
<td>Dual reaction</td>
<td>Not done</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
<tr>
<td>N.S. F, 33</td>
<td>Asthma since childhood, hay-fever</td>
<td>6,000</td>
<td>Dual reaction</td>
<td>Many pos.</td>
<td>Neg.</td>
<td>Pos.</td>
<td>Present</td>
<td>Pos.</td>
</tr>
</tbody>
</table>

*Histoplasmin, blastomycin, coccidioidin, O.T. 1/1,000.
**Culture for *A fumigatus*.

DIS. CHEST, VOL. 55, NO. 5, MAY 1969
As spores of *A. fumigatus* and other species are ubiquitous in their distribution and are present perennially, they are frequently inhaled and expectorated by the population at large, so that isolation and culture cannot, by itself, be taken as proof of a causal relationship to the clinical manifestations. From 2,008 patients with various respiratory diseases, sputum cultures were positive for *A. fumigatus* in 145 cases. Twenty-seven of these patients, 23 of whom were asthmatic, were further studied by direct bronchial challenge testing. Sixteen gave positive and 11 negative results when subjected to an aerosolized extract of *A. fumigatus*.

Clinical features of the 16 patients who gave positive bronchial test reactions included asthma, recurrent febrile episodes, transient radiologically demonstrated shadows, sputum and blood eosinophilia, firm plugs, bronchiectasis at the site of previous shadows, and positive skin test reactions to *Aspergillus* extracts as well as to other allergens. The patients reported here showed many of these features; none, however, has had bronchial challenge tests.

The presence of precipitating antibodies against extracts of *A. fumigatus* in the serum of patients suffering from hypersensitivity pulmonary aspergillosis was reported in 1959 by Pepys et al. This form of antibody was demonstrated by double diffusion in agar gel, with one or more lines appearing. The sputum of all 13 patients in his group with these antibodies contained *A. fumigatus*. Ten of 13 gave positive skin tests and seven of 13 positive bronchial challenge tests using extracts of *Aspergillus*. One patient with an aspergilloma and one asthmatic subject had demonstrable precipitating antibodies without positive skin or bronchial tests. No precipitins were found in the serum of 14 other patients who also had *A. fumigatus* in the sputum and showed immediate hypersensitivity to the extracts, nor in a group of patients without evidence of hypersensitivity to the fungus, either with or without the *A. fumigatus* in the sputum. In another study Longbottom found that 9 percent (29/307) of patients with asthma only, 63 percent (59/93) of patients with asthma, pulmonary infiltrations and blood eosinophilia, 98 percent (58/57) of aspergilloma patients, and 8 percent (14/185) of patients with other lung conditions had demonstrable precipitating antibody against *A. fumigatus* in their serum. Recent personal communication (Longbottom, J. L., Nov. 1967) confirmed that over 90 percent of patients with the syndrome described above were shown to have precipitating antibodies when nonreactive serum was concentrated by a factor of 3 to 4. All of the patients described above have shown the presence of these antibodies to one or more extracts of *A. fumigatus*, by modified gel diffusion techniques.

The demonstration of the patient’s sensitivity to *A. fumigatus* is of prime importance in confirming the diagnosis. Skin tests with extracts from the fungus initiates an immediate wheal and flare reaction, usually associated with the presence of reaginic antibodies. These reactions are maximal in 15 to 20 minutes and fade by about one hour, to be followed in 3 to 12 hours by a second response consisting of local swelling which extends over a variable area with a definite, but poorly defined, central induration. This second phase, associated with precipitating antibodies, is maximal by 24 hours.
HYPERSENSITIVITY BRONCHOPULMONARY ASPERGILLOSIS

All of the original cases reported exhibited a persistent peripheral blood eosinophilia of over 1,000 per cu mm. The patients reported above, with the exception of patient R. M., have also shown peripheral blood eosinophilias often to levels of over 1,000 per cu mm. None, however, has had a persistent eosinophilia, as each showed a dramatic fall in the count upon exhibition of corticosteroid therapy, which was apparently not used in the management of Hinson's cases. The case of patient R. M. may be similar to the cases reported by Sanerkin in which eosinophilia was not noted.

It seems reasonable to speculate on the pathophysiology of this condition. Bronchial asthma related to A fumigatus as an allergen would seem no different to allergic asthma such as that related to pollens or animal danders. The nature of the process which gives rise to reagin is obscure, although it is believed currently that reagin is an IgE. The process whereby A fumigatus gives rise to precipitins is also not clear, nor is it known whether different antigenic determinants are involved. It must be presumed that the fungal antigen gains access to the regional lymph nodes giving rise to a precipitin which in this case is IgG. Once circulating antibody is present, an Arthus type reaction may be produced locally following injection of the extract. Thus, upon appropriate bronchial challenge with the fungus an immediate, reagin-mediated reaction occurs. This gives the clinical picture of asthma with outpouring of bronchial exudate and narrowing of larger and blocking of smaller bronchioles. The fungus trapped in this exudate, if not expectorated, begins to grow. Gaseous movement

DIS. CHEST, VOL. 55, NO. 5, MAY 1969

Figure 7. High power view of vessel in Figure 6 demonstrating the perivascular infiltration with granular (eosinophil) cells.

Figure 8. Immunofluorescence study of this area, using anti-IgG, demonstrating localization of complexes around the vessel.
in the alveoli is prevented distal to the plug, with resultant collapse of these segments, trapping of secretions, and the x-ray picture of localized segmental consolidation. Polysaccharide antigens from the fungus may gain access to the interstitial tissues surrounding the plug, with antigen-antibody complexes and some components of complement forming in the perivascular area. This type of reaction has been demonstrated here by immunofluorescence in the skin biopsies and is probably similar to that in the lung. This situation differs from some forms of immunologic injury to kidney in which circulating antigen-antibody complexes locate, there being as yet no evidence for the existence of circulating antigen-antibody complexes in hypersensitivity bronchopulmonary aspergillosis. It is known that allergen reagin complexes are associated with a marked eosinophilia in the surrounding tissue, and pulmonary eosinophilia can be achieved in guinea pigs and hogs by injecting antigen into the vena cava. When the plugs are expectorated, the involved segment of lung is able to reexpand and drain again, and the intense antigenic challenge is removed from the area. Following this the inflammatory response settles and heals by fibrosis of the area. Once damaged, this segment is prone to recurrence of the events, thus the recurring shadows in the same areas. With each additional amount of scarring of the bronchial wall there is an increased amount of distortion and this eventually may lead to the characteristic pattern of a saccular bronchiectasis with normal peripheral filling unless the peripheral portions have also been damaged secondarily by infection. The fibrosis on healing also gives the reticular pattern seen on x-ray examination of previously affected segments.

In the spectrum of hypersensitivity lung diseases, this syndrome should be distinguished from several other syndromes associated and possibly mediated by precipitating antibodies. In bird fancier’s, pituitary snuff takers, and farmer’s lung patients, asthma may or may not be present but the main pulmonary reaction is at the alveolar level rather than in the bronchioles. The reduction of diffusing capacity is more prominent than the increased airways resistance in these syndromes, whereas in hypersensitivity aspergillosis the reverse is the case during exacerbations. It seems probable that the syndrome herein described is but one variant of the so-called Loeffler’s syndrome, in which the antigen is known.

Therapy of this syndrome revolves around the use of the corticosteroid drugs. They are used in a dual capacity—antiasthmatic and anti-inflammatory. Just as the use of these agents inhibits to a great degree the second phase of the dual skin reaction to antigen, so it seems to inhibit the second phase of the pulmonary reaction. By contrast, although it does not inhibit the immediate skin test reaction, it does suppress the asthmatic (bronchospasm) reaction. This would conceivably relate the recently described effect of cortisol in suppressing the release of kinins from granulocytes. Several regimens have been tried, with perhaps the most satisfactory being to give the patient a dose high enough both to stop the progress and to initiate the regression of the syndrome. Once under control, the dose should be reduced to the lowest level which, over the long period, keeps the patient relatively symptom-free. This will often be achieved with levels just at or above physiologic production rates. Maintenance of this regimen over many years is probably justified, with prompt elevation of the dose at any suggestion of a flare-up. These periods may also be covered by the use of broad-spectrum antibiotic if there is evidence or suspicion about secondary bacterial infection. Although injections of extracts of A fumigatus are well tolerated by asthmatic patients, the majority of patients with this syndrome react adversely, giving increasingly large local and occasionally late systemic reactions, even when the concentration of extract used is very low. (Patient N. S. reacted in this manner.) Attempts have been made to treat this condition by the use of inhalations of fungistatic and fungicidal drugs. While this may be of use in the immediate situation, this form of therapy does nothing to alter the response of the patient to the fungus; thus when next challenged with a sufficient dose, he may react in the predicted fashion with no check being placed on the response.

ADDENDUM: Since this report was compiled, five more patients with this syndrome have been studied. All showed the complete picture of the illness, but more showed the mucus plug complication.

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DIS. CHEST, VOL. 55, NO. 5, MAY 1969
HYPERSENSITIVITY BRONCHOPULMONARY ASPERGILLOSIS


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A PHENOMENAL ENCYCLOPEDIA OF ANCIENT ROME

The Natural History of Pliny the Elder (23–79) was the accepted compendium of science for the literate Romans of the empire, was the major arsenal of facts used by the Christian writers in the patristic period, was the basis of scientific information of all medieval compilers until the ascendency of Aristotle in the period of scholasticism, and even contested Aristotle's popularity in scientific matters. His Natural History is much the most complete repertory of antique learning, scientific and cultural, which has been preserved.

Pliny was a state official and naval officer. He had little save his nights to devote to the acquisition of scientific data. He stated that he had read two thousand books in the course of his investigations. He had scientific tracts read to him while he ate, and often dictated his materials from his bath.


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