Thoracic aspergillosis (part I)

Overview and aspergilloma[1]

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With the increase in the number of patients receiving immunosuppressive therapy, the incidence of fungal infection is also on the rise. The fungus *Aspergillus*, a ubiquitous saprophyte, can produce pulmonary as well as systemic infection in several different forms. These include aspergilloma, primary pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, invasive aspergillosis, and disseminated aspergillosis. The manifestations and treatment of these forms of infections vary greatly from one to another. In part I, the authors review the broad spectrum of thoracic aspergillosis with comments on the localized form, aspergilloma.

Index terms: Aspergillosis · Fungi · Review articles

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Aspergillosis is produced by several different species of *Aspergillus*. *Aspergillus* occasionally may produce human infection. The lung is the most common site of infection. Aspergillosis is associated with a wide variety of clinical manifestations. These include a disseminated form, which develops in immunosuppressed patients; an allergic form, which represents a complex immunological reaction of the host to a relatively innocuous exposure to a noninvasive *Aspergillus*; and a localized form, aspergilloma, which generally is considered to be an opportunistic infection in individuals with underlying pulmonary disease. There also is a rare primary form, which develops in apparently normal hosts who have been exposed to a massive inoculum of *Aspergillus*. The purpose of this paper is to review the broad spectrum of thoracic aspergillosis with comments on the localized form, aspergilloma.

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History

Ramazzini,[1] in 1713, described the development of respiratory symptoms in workers who had been exposed to the dust of overheated cereal grains, but did not relate these symptoms to exposure to a specific microorganism. Micheli,[2] in 1729, first described the stalks and spore heads of aspergilli. He noted that the spore chains radiated from a globelike structure. The name *Aspergillus* was chosen because of the similarity of these spore-bearing heads to the brush (aspergillum) which Micheli, as a priest, employed for sprinkling holy water. *Aspergillus* was found to be invasive in animals by Mayer and Emmert,[3] who discovered the organism in the lungs of a jay in 1815. According to Hinson,[4] Jäger, in 1816; Heusinger, in 1826; Deslongchamp, in 1841; and Robin, in 1853, described *Aspergillus* infection in other birds. Rivolta, in 1887, as cited by Hinson,[4] discovered the organism in the laryngeal swelling of a horse.

Human infection probably was first described by Bennett,[5] in 1842, in a patient with tuberculosis. The fungus isolated in this case was believed to be *Penicillium*, but may have been *Aspergillus*. As cited by Hinson,[4] a similar case was described in the same year in Germany by Rayer. Also noted by Hinson,[4] Küchenmeister, in 1855, discovered a fungal infection in patients with cancer of the lung. The first definite case of human *Aspergillus* infection was described by Sluyter,[6] in 1847, in a woman who died of a chest illness. She had a fungal mass in a lung cavity. The fungus originally was reported as "mucor," but later was recognized as *Aspergillus*. In 1856, Virchow[7] described four patients with aspergillosis who died of other causes and in whom secondary infection by *Aspergillus* developed in preexisting lung lesions. Friedreich,[8] in the same year, and according to Hinson,[4] Furbringer, in 1876, reported growth of the fungus in tuberculous cavities. Cohnheim,[9] in 1865, identified the fungus in the alveoli of a man who had suffered from pulmonary infarction.

In 1887, Osler[10] reported the case of a 19-year-old woman who for 11 years, at three-month intervals, had expectorated dark bodies, which consisted almost entirely of mycelia and spores of *Aspergillus*. In 1890, Wheaton[11] described a two-year-old child who died of pneumonia and had *Aspergillus* in the lungs and lymph nodes.

In 1890, at an international conference in Berlin, Dieulafoy et al[12] described aspergillosis in three pigeon crammers (feeders) who had had chronic symptoms. They attributed the symptoms to infection with *Aspergillus* and called it *maladie des graveurs*. The disease was similar to chronic pulmonary tuberculosis, with symptoms of dyspnea, cough, purulent sputum, and repeated minor episodes of hemoptysis. The sputum did not contain acid-fast bacilli, but contained *Aspergillus fumigatus*. The authors suggested that the grain used to feed pigeons, known to be heavily contaminated with the fungus, had produced the disease. They named the disease *pseudotuberculose mycosque*.

In 1893, 1895, and 1897, Rénon[13,14] reported two cases in hair combers who had used rye flour for removing grease from hair before fashioning wigs. These cases, in addition to those of Dieulafoy et al,[12] led Rénon to consider aspergillosis to be a trade disease among those involved in the artificial feeding of pigeons and those who worked with hair and hair products. The infecting agent was identified as *A fumigatus*, and rarely, *Aspergillus niger*, the spores of which might be mingled with grain, seeds, or flour. Rénon referred to primary and secondary aspergillosis, the latter consisting of instances in which the fungus was found in association with carcinoma, bronchopneumonia, or tuberculosis. The evidence cited to support the existence of a primary form of infection was the inability to discover tubercle bacilli in most of the cases and the death of rabbits and pigeons 10–20 days after inoculation with *A fumigatus*. However, there was no supporting postmortem evidence.

Boyce,[15] in 1892, and Arkle and Hinds,[16] in 1896, reported two more cases, the former in association with thrombosed vessels. As cited by Hinson,[4] Mirsky was the first to identify *Aspergillus versicolor* in the sputum in 1903, and Steele[17] reported similar findings in 1926. Holden[18] described *Aspergillus nidulans* in the sputum in 1915, and Bethune and Moffatt[19] reported *A niger* infection in 1933. Wahl[20] was first to discover *Aspergillus flavus* in the sputum in 1928. In 1912, Raether[21] reported that a large inoculum of the fungus was required to produce disease in man because man was relatively resistant to *Aspergillus* infection. Kleberger,[22] in 1920, and Kaufmann,[23] in 1922, suggested that grippe and diabetes might be predisposing causes of pulmonary aspergillosis.

In 1924, pleural cavity infection with *Aspergillus* was described by Cleland,[24] who reported a

patient in whom fungal infection followed an empyema produced by a gunshot wound. Further cases were reported by Barlow,[25] Golebiowski,[26] and Sochocky.[27]

In 1887, Popoff, as cited by Hinson,[4] described an allergic variety of aspergillosis in a 21-year-old woman who had symptoms of asthma and whose sputum did not contain acid-fast bacilli, but consisted of many casts comprised of *Aspergillus* mycelia and spores. In 1897, Rénon described an association between asthma and aspergillosis, and v. Leeuwen[28] et al, in 1925, drew attention to this association. Reports by Hammerman et al,[29] in 1925; Brenton,[30] in 1930; Flood,[31] in 1931; and Brown,[32] in 1932 and 1936, confirmed the association. In 1936, Feinberg[33] demonstrated that between 1% and 20% of asthmatics have positive skin tests to *Aspergillus* extract. In 1952, Hinson et al[4] reported three patients with symptoms of recurrent asthma, pulmonary infiltrates, fever, eosinophilia, and plugging of bronchi produced by *A fumigatus* hyphae. It was at that time that allergic bronchopulmonary aspergillosis was recognized.

Aspergillus species are found more commonly in the sputum of patients with asthma than in those with other lung diseases. A large series of patients with allergic aspergillosis was reported by Campbell and Clayton,[34] in 1964, who described 87 patients with allergic bronchopulmonary aspergillosis and 27 with probable allergic bronchopulmonary aspergillosis. In 1968, Henderson[35] reported 32 such patients. Immediate skin reaction, bronchial hypersensitivity, and precipitating serum antibodies to *A fumigatus* extract were demonstrated by Pepys et al,[36] in 1959, and Longbottom et al,[37] in 1964. Also in 1964, Campbell and Clayton[34] reported positive skin tests in 99% and precipitins in 69% of patients with allergic aspergillosis. In 1966, Pepys[38] emphasized the possible role of precipitins in the pathogenesis of the disease. In 1968, Patterson and Golbert[39] described the first case of allergic bronchopulmonary aspergillosis in the American literature.

According to Villar and Pimentel,[40] Figuerra first reported aspergilloma in the Portuguese literature in 1862. In 1936, Leon-Kinderberg et al[41] were the first to report aspergilloma simulating bronchogenic carcinoma. The French literature cites Dévé,[42] in 1938, as the first to report aspergilloma, which he called *mega-mycetome intrabronchectasique*. Metras and Thomas,[43] in 1946, and Monod et al,[44] in 1952, attributed the formation of aspergilloma to the dilatation of a normal bronchus as a result of the pressure of a growing fungus colony, which had implanted on it. Levin,[45] in 1956, who reviewed the literature and reported four cases, and Vellios et al,[46] in 1957, disputed this theory and suggested that the fungus is a saprophyte that fortuitously invades preexisting pathologic foci.

In 1958, Foushee and Norris[47] reported a case of primary cavitary aspergillosis limited to the right upper lobe, but Orie et al,[48] in 1960, and Villar et al,[49] in 1963, doubted that primary aspergilloma exists. They suggested that there is a preexisting lung cavity or cyst in which the fungus grows saprophytically to produce the fungus ball. The role of bronchiectasis in the pathogenesis of secondary aspergilloma was established by Vantrappen et al,[50] in 1959, who demonstrated small fungal masses in bronchiectatic sacs. Goldberg,[51] in 1962, and Macartney,[52] in 1964, demonstrated enlargement of aspergillomata and their cavities. In 1973, Pepys[53] suggested that bronchial dilatation was due to the precipitin-mediated Arthus-type reaction in the bronchus, and that the aspergilloma was the source of the antigen.

Occupational history

Aspergillosis as an occupational disease in pigeon crammers, wigmakers, fur cleaners, farmers, and others exposed to large numbers of spores was described by Rénon,[13,14] in 1893, 1895, and 1897; Dieulafoy et al,[12] in 1890; Schneider,[54] in 1930; Bethune and Moffatt,[19] in 1933; Cannon,[55] in 1935; Stolow,[56] in 1939; Rubin,[57] in 1947; and Davidson,[58] in 1948. In 1945, Coe[59] reported the only case of aspergillosis for which financial compensation was awarded. The patient was a stockyard worker who had chronic respiratory symptoms that developed after he had worked in contact with hay, grain, corn, and straw for more than 20 years. Considerable doubt concerning the validity of aspergillosis as an occupational disease was raised by Macartney,[52] in 1964; he noted that the only indisputable fact emerging from all previous reports was that the patients had been engaged in occupations that had exposed them to a high likelihood of fungal contamination. Riddell and Clayton,[60] in 1958, and Pepys et al,[36] in 1959, reported that 7% of sputum cultures in patients with a wide variety of chest diseases revealed *A*

Table 1. Classification

Noninvasive aspergillosis
Aspergilloma
Allergic bronchopulmonary aspergillosis
Mucoid impaction
Bronchocentric granulomatosis
Eosinophilic pneumonia
Extrinsic allergic alveolitis
Invasive aspergillosis
Primary invasive aspergillosis
Secondary invasive aspergillosis
Disseminated aspergillosis

fumigatus, indicating that the presence of *A fumigatus* does not confirm its pathogenic role. In 1946, Hunter and Perry[61] studied bagasse shredder operators, and in 1961, Stallybrass[62] investigated grain millworkers, in whose occupations the *Aspergillus* spore count in the environment is extremely high, but failed to demonstrate an increased incidence of pulmonary aspergillosis.

Epidemiology

The genus *Aspergillus* belongs to the order Moniliales and the class Deuteromycetes (higher fungi). *Aspergillus* is a ubiquitous saprophyte,[63] which is widely distributed in nature. It exists in soil, decaying vegetation,[64,65] rotted wood,[64,65] fur,[65] swimming-pool water, flour, human hair,[66] common foods,[42,67] hospital wards, and as a common contaminant in bacteriology laboratories.[63,68] It is a common pathogen of birds.[64]

Foodstuffs may be invaded by aspergilli, and foods that are well preserved against decomposition by bacteria support the slow growth of *Aspergillus* at low temperatures. Approximately 350 species of *Aspergillus* have been identified[66]; these have a worldwide distribution. Human infection is most commonly produced by *A fumigatus*. Other species, which are occasionally pathogenic to man, are *A flavus*,[69] *A niger*,[63,70] *Aspergillus terreus*,[71] *A nidulans*, *Aspergillus carneus*, *Aspergillus sulphureus*,[70] *Aspergillus glaucus*,[72] *Aspergillus oryzai*, and *Aspergillus sycowi*.[52] Aspergillosis is found in all races.[65] It is more common in adults than in children, and in males more than in females.[65] The respiratory tract, external auditory canal, skin, and nails are the most common sites of infection. Occasionally, when the infection becomes disseminated, meningitis, encephalitis, endocarditis, and involvement of the paranasal sinuses and orbit may occur.

Aspergillus species are filamentous fungi producing airborne spores. The number of *Aspergillus* spores in the air increases significantly during the autumn and winter months.[34,73]

Because of the wide distribution[65] and the perennial presence of *Aspergillus*,[67] the fungal spores probably are inhaled and expectorated by the population at large.[36,67,74] Since *Aspergillus* is a common contaminant of sputum and may, at times, be present in the respiratory tract without harmful effects, *Aspergillus* cultured from the sputum does not establish it as the organism responsible for clinical manifestations in a particular patient.[34,36,52,65,67,68,75,76]

The manifestations of aspergillosis vary in severity from saprophytism to the production of fulminant fatal infection. The invasive capacity of the spores depends on the quantity of the inhaled spores and the physical condition of the person who has inhaled them.[65]

Aspergillus may be grown on many media.[64] The most useful medium for isolation of the fungus is 2% malt extract in 2% agar without added peptone or glucose, but containing antibiotics. Blood agar or brain/heart infusion agar also are adequate for the growth of *Aspergillus*. Sabouraud's glucose and maltose agars often are used.[75,76] However, these are not entirely satisfactory since growth of the fungus is predominantly vegetative.[77]

To culture aspergilli, it is advisable to collect sputum specimens in sterile glass containers. *A fumigatus*, if present, usually will appear within 48 hours, but it may be necessary to maintain the culture for as long as seven days. The culture may be incubated at 37°C–45°C, which may aid in differentiating *Aspergillus* from other fungi. Some cultures are grown on media containing streptomycin[65] or chloromycetin and penicillin,[65,77] since aspergilli are resistant to these antibiotics, which serve to eliminate bacterial contamination of the culture. An adequate oxygen tension is essential to the development of spores, but mycelia grow under relatively anaerobic conditions.[52]

The *Aspergillus* colony is a white mass of interweaving mycelial threads,[4,64] from which occasional cells, known as "foot cells," enlarge.[77] The foot cells produce a shoot, which elongates upward (conidiophore) and bears a swollen vesicle

at its free extremity. From this vesicle, shorter stalks arise like the bristles of a brush (phialides). Each stalk bears a row of conidia or spores, which may be colored, producing varying tints to the mature colonies, from smoky green to gray or purplish-gray.[4,20,77] In tissues, the mycelia seldom bear conidia or conidiophores; since these are necessary for identification, it is impossible to identify the organism or to determine its species without isolation on artificial media.[20] The ability to grow on many different substrates under a wide range of environmental conditions has enabled some aspergilli to colonize living and dead animal tissue. The normal life cycle of aspergilli in nature includes spore germination, substrate colonization, fructification, and airborne dissemination

Classification

In 1952, Hinson et al[4] classified aspergillosis; since then, various modified classifications have been proposed. *Table 1* lists the currently recognized forms of pulmonary disease produced by *Aspergillus* species. Mediastinal involvement may occur in both primary and secondary invasive forms of the disease.

ASPERGILLOMA

The essential feature of a mycetoma is a ball of mycelia lying free in a pulmonary cavity, which communicates with the bronchial tree. It usually is regarded as a saprophytic manifestation of a fungus growing in a preformed and poorly drained lung space. Mycetoma has occasionally been described with other fungi, including *Candida*,[45,78] *Coccidioides immitis*,[79] Mucorales,[80] *Cephalosporium*,[81] *Metschnikowia pulcherrima*,[71] *Penicillium* species,[82] and *Allescheria boydii*,[83,84] but these cases remain controversial.[82] Aspergilloma is the most frequent form of aspergillosis.[85] Macpherson[86] found aspergilloma in 0.01% of a population of 60,000 who had undergone radiography performed during the preceding 10 years. The incidence of aspergilloma in the general population is unknown, but has been estimated to be 0.01%–0.02%.[82,87] Pepys et al[36] found a 0.02% incidence of aspergilloma after studying 2,080 patients. In a series of 360 cases of pulmonary aspergillosis, Eckelmans[88] found 67.5% to have aspergilloma.

The most common disease antecedent to the development of an aspergilloma is tuberculosis. *Table 2* lists the conditions predisposing to aspergilloma. Rzepecki et al,[89] in a review of 113 cases of pulmonary aspergillosis, found a 72% (85 cases) incidence of pulmonary tuberculosis as the predisposing disease. In most of the patients with pulmonary tuberculosis, the duration of infection was more than five years, but in more than 30 cases, the history suggested a duration of 10, 15, 20, and even 30 years. Unnecessarily prolonged or erroneous chemotherapy was found to be a common factor in these patients. Minárik et al[90] reported an 18% incidence of aspergilloma in patients with underlying pulmonary tuberculosis. In most of the patients, aspergilloma developed within the first three years of debacillization. Villar and Pimentel,[40] in a series of 68 cases, reported a 50% incidence of thoracic aspergilloma in patients with underlying pulmonary tuberculosis. During 1964–1965, the Research Committee of the British Thoracic and Tuberculosis Association reviewed 544 patients who had had sputa negative for tubercle bacilli for at least a year and who had a residual cavity of 2.5 cm or more in diameter.[91] These patients were resurveyed after three to four years. In the initial survey, 11% of the precipitin-positive patients had definite radiological evidence of aspergilloma, and 4% were considered to have probable aspergilloma. At the time of the second survey, the incidence had changed to 17% and 3%, respectively.[92] The highest maximum incidence of

Table 2. Diseases predisposing to the development of aspergilloma

Tuberculosis
Sarcoidosis
Pneumoconiosis
Pulmonary infarction
Histoplasmosis
Healed abscess cavities
Bullous emphysema
Ankylosing spondylitis
Congenital heart disease
Bronchiectasis
Allergic bronchopulmonary aspergillosis
Pneumothorax
Radiation fibrosis
Postlobectomy (bronchial stump)
Invasive aspergillosis
Blastomycosis
Cryptococcosis
Cavitary bronchogenic carcinoma
Congenital cysts
Alveolar proteinosis

Aspergillus infection occurred in those who had had cavitary tuberculosis for 7–11 years. McCarthy and Pepys,[93] in a series of 28 patients with aspergilloma, found that 25% (7 patients) had a history of pulmonary tuberculosis; similar observations have been made by others.[48,82,87,93–106]

The second most common predisposing disease is sarcoidosis. In patients with sarcoidosis, cystic cavities frequently develop in the upper lobes. Aspergilli often proliferate to form a fungus ball in such patients.[107] Fougner and Gjone[108] were the first to recognize the association between sarcoidosis and aspergilloma. Israel and Ostrow[107] reported 10 patients with sarcoidosis in whom aspergilloma developed, and many others report the association between sarcoidosis and aspergilloma.[88,93,98,107,109–111]

Aspergilloma has also been noted to be a sequela of pulmonary infarction, histoplasmosis, pneumoconiosis, ankylosing spondylitis, congenital heart disease, healed abscess cavities, radiation fibrosis, bullous emphysema, pneumothorax, cavitary bronchogenic carcinoma, bronchiectasis, alveolar proteinosis, postlobectomy bronchial stump, blastomycosis, cryptococcosis, echinococcus cysts, allergic bronchopulmonary aspergillosis, invasive aspergillosis in compromised hosts, and congenital pulmonary cysts.

Some investigators believe that the development of aspergilloma may take place in the absence of preexisting lung disease.[47,73,112,113] Sawasaki et al[114] presented experimental evidence in rabbits for a primary check valve mechanism in the production of pulmonary cavitary aspergilloma. This was produced when a fungal mass resulting from injected spores grew on an ulcerate bronchial wall, with an associated induced stenosis of a pulmonary or a bronchial artery. However, this concept remains highly controversial.

Antibiotics and corticosteroids have been thought to promote fungal growth in man. Minárik et al[90] observed stimulation of the growth of *Aspergillus*, and subsequent enlargement of an aspergilloma, in 5 patients who had received antibiotics and corticosteroids. The effect of corticosteroids and antibiotics on this fungal growth, however, is disputed by other investigators.[40,93,106]

Pathogenesis and pathology of aspergilloma

Villar et al[102] divided the life cycle of aspergilloma into five stages.

1. *Initial stage.* In this stage, the sporulating conidiophores grow on the wall of a cavity within an air space and subsequently peel off to form a fungus ball. Necrotic lung tissue is colonized by the fungus, which forms vegetative-type hyphae, which are always viable. The process varies with the degree of host resistance. In this stage, clinical symptoms or radiological signs are rarely observed. In most cases, the mycetoma develops slowly, but rapid growth has occasionally been observed in which fungus balls of 3.0 cm or more in diameter develop during the course of a few weeks.[82,115]

2. *Second phase or fully developed stage.* In this stage, the fungus both grows and dies and the mycetoma is comprised of both living and dead fungus. The growing fungus forms one or more brownish balls as mycelia and debris are shed. The different staining characteristics of the fungus, fragmentation, softening, and deposition of calcium differentiates living from dead fungus. The epithelial lining of the cavity is rarely maintained, and its size increases as a result of the growth of mycelia and the inflammatory reaction caused by mycotoxins. Subsequently, fibrotic scarring develops following the formation of granulation tissue. The fungus grows in a partially filled cavity, causing the mycetoma to grow over a period of time.

3. *Third phase or calcified aspergilloma.* When the fungus dies, it undergoes regressive changes in structure, leading to softening, fragmentation, and focal calcification. In this phase, instead of remaining focal, the calcification involves the greater part of the fungus ball, which then becomes completely transformed into a calcified structure. This is believed to take place only in patients in whom the dead fungus remains within a cavity and subsequently forms a calcified aspergilloma. Pimentel[116] reported nine cases of aspergilloma with evidence of calcification. Villar et al[102] reported four of 30 aspergillomas that had calcified. Nime and Hutchins[117] observed calcium oxalate deposition in the fungus ball in 11 patients with aspergilloma and suggested that the presence of calcium oxalate deposits depends on the *Aspergillus*, which is known to produce oxalic acid. The oxalic acid from the fungus combines with the calcium from the patient, producing deposits of calcium oxalate crystals adjacent to the mycelium. These investigators and others suggested that the tissue necrosis adjacent to the mycelium is due to oxalic acid deposition.[117,118]

4. *Fourth or residual stage.* This stage is identified in two forms: (*a*) abscesses containing only fragments of mycelia and (*b*) broncholiths and cavernoliths found in bronchial dilatations of pulmonary cavities as tiny concretions, either free or incorporated within the granulation tissue of the cavity wall.

5. *Fifth or abortive stage.* This form is considered pathologically similar to the residual form; the only difference is that it is not preceded by the fully developed stage.

Rarely, a patient with aspergilloma may experience progressive symptoms with increasing lung infiltrates. At necropsy, these patients have been found to have invasive aspergillosis.[35,47,71,101,119-121] However, Varkey and Rose[101] believe that the risk of aspergilloma progressing to invasive aspergillosis or producing hematogenous dissemination of the fungus is negligible, occurring only in patients who receive immunosuppressive and cytotoxic drugs.

The cavity in which the pulmonary aspergilloma forms often has an intact epithelial lining. The fungal colony acts as a foreign body, which keeps the cavity open, thus preventing healing of the underlying lung disease. In the case of erosion, the cavity wall usually is lined by chronically inflamed granulation tissue, which has no specific histological features. Multinucleated giant cells, some of which enclose fungal hyphae, sometimes may be seen. This is due to a phagocytic response to the incorporation of fungal elements in growing granulation tissue and does not indicate invasion by the fungus.

Spontaneous disappearance of aspergilloma has been observed on radiographs by many investigators.[92,107,122-124] Nevertheless, the actual frequency of this phenomenon is difficult to determine. In two cooperative studies, Davies,[125] in 1970, and Hammerman et al,[123] in 1973, found spontaneous lysis in 10% of cases. Varkey and Rose[101] reported the disappearance of aspergillomas in 4 patients after following 8 untreated patients for an average of 50 months.

Clinical features (*Table 3*)

Aspergilloma, in general, does not produce an adverse effect on health and body weight. This is particularly true in patients who do not have any allergic diatheses.[45,77,126] The lesions may remain stable for long periods of time.[45] The diagnosis usually is made when the patient is in the fourth or fifth decade of life. The incidence of aspergilloma is higher in males than in females.[40,93] Villar et al[40] reported an age incidence between 10 and 63 years, with the highest between 30 and 40 years. In 8 patients reported by Laustela,[105] ages ranged between 20 and 47 years, and sex distribution was equal. Reddy et al[121] reported an average age of 55 years and a male to female ratio of 4 to 1. The apical regions of the lung usually are involved by aspergilloma except in patients predisposed by allergic bronchopulmonary aspergillosis in whom the area most commonly involved is the midlung field. Atopic patients appear to suffer from generalized symptoms more than those who are not atopic. Davies and Somner[106] described two patients who had chronic ill health, weight loss, dyspnea, copious purulent, and frequent bloodstained sputum, without evidence of bacterial infection. Similar constitutional symptoms have been noted by other investigators, particularly in patients with hypersensitivity to *Aspergillus*.[42,93,96,101,127] Patients with atopy have associated allergic bronchopulmonary aspergillosis with symptoms of asthma and large quantities of sputum production. Superimposed bacterial infection may be present and may be responsible, at least in part, for the sputum production in these patients.[93]

Table 3. Clinical features of aspergilloma

Hemoptysis
Cough and sputum
Clubbing
Fever
Malaise
Weight loss
Reactive airway disease
Pleuritis (uncommon)

The most common and important clinical feature is hemoptysis.[99] This may range from infrequent small episodes of blood-tinged sputum to massive and fatal exsanguinating hemorrhage.[48,88,92,93,98,107,111] The incidence of hemoptysis varies between 50% and 80%. McCarthy and Pepys[93] reported an 82% incidence of hemoptysis in a series of 28 patients. Levin[45] found a 63% incidence in 27 patients. Villar and Pimental[40] suggested that patients with calcified aspergilloma have a higher incidence of hemoptysis; they attributed this to traumatization of vascular granulation tissue by the movement of the concentrations within the cavity, as the result of cough and respiratory movements.

Table 4. Modalities used to determine a diagnosis of aspergilloma

Radiology
Immunology
Mycology
Strontium isotope scanning
Transbronchial or percutaneous biopsy

Hemoptysis developed primarily in patients harboring live fungi.[40] Solit et al[98] have reported five deaths due to massive hemoptysis in 32 patients with aspergilloma. In 36 patients with aspergilloma, whose course was assessed by Karas et al[128] over a period of one year, 8 of 23 patients with hemoptysis were considered to have life-threatening hemorrhage. Approximately 4% of patients died from hemoptysis and 5% of patients required surgical resection. The incidence of death was about three times higher than expected.[129] Once hemoptysis has occurred, the possibility of a fatal hemorrhage may be as high as 30%.[111] The cause of hemoptysis is disputed. Villar and Pimentel,[40] in 1962, and Pimentel,[116] in 1966, suggested that it was due to mechanical movement of the fungus ball within the cavity, traumatizing highly vascular angiomatous granulation tissue. Macartney[52] suggested that a hemolytic endotoxin isolated from *Aspergillus* might be responsible for hemoptysis. Others believed that a trypsinlike proteolytic enzyme and an anticoagulant produced by *Aspergillus* might be responsible for the bleeding.[34,107]

Other symptoms include cough with sputum production, hemoptysis with or without asthma, and clubbing of the fingers, which is observed in approximately 33% of patients. McCarthy and Pepys,[93] in a series of 28 patients, reported cough with sputum production in 100% of the cases, asthma in 43%, flecks or brown pieces in the sputum in 22%, clubbing in 29%, airway obstruction in 43%, and localizing signs, including a dull percussion note, bronchial breath sounds, and crepitation in the region of the lesion, in 86%. Levin,[45] in a series of 27 patients, did not detect fever, pain, weight loss, or asthma. Cough with expectoration, however, was the second most common feature. Others have noted similar constitutional symptoms, particularly if the patient was hypersensitive to *Aspergillus*.[101,127] Slowly progressive dyspnea occurs occasionally.[106] It may result from thickening of the pleura over the cavity when aspergilloma appears.[77] Obstructive pneumonitis may occur if the fungus ball obstructs the bronchus leading from the cavity.

Diagnosis

The various diagnostic modalities that may be used to assist in the diagnosis of aspergilloma are noted (*Table 4*).

Roentgenography is probably the most important diagnostic tool. A posteroanterior chest radiograph, followed by laminography of suspected areas, has proved valuable. Pesle and Monod[130] described a characteristic radiographic sign: a rounded, dense opacity occupying some or most of the cavity and fully or partially surrounded with a crescent patch of air (Monod's sign) (*Figure*). This is the most frequently found radiological abnormality indicating aspergilloma.[49,51,131] According to Vellios et al,[46] Dévè, in 1938, was the first to use this finding when making a diagnosis. The mass may move within the cavity as the patient changes position, indicating that it is free within the cavity.[131,132] The air space may not be detected on the chest radiograph if the fungus ball has completely filled the cavity. In such cases, laminography may be helpful.[51] The aspergilloma cavity may be rounded, oval, elongated, or irregular. The most common abnormality is the round or oval cavity. The irregular form is most likely to be associated with preexisting lung disease.[131] Although such a radiograph is characteristic of aspergilloma, it may also be seen rarely in a resolving blood clot in a cavity, a pulmonary hydatid cyst, a lung abscess containing necrotic tissue, a neoplasm with peripheral cavitation, and in liquefied infarcts.[131] Irregular calcified densities may be present within the cavity.[51,116] Pleural thickening overlying the cavity also has been described. Libshitz et al[133] have noted that pleural thickening is a frequent manifestation of *Aspergillus* superinfection in cystic and cavitary pulmonary disease, that it may precede the appearance of the aspergilloma by two or three years, and that, when seen, it should suggest the possibility of *Aspergillus* superinfection. Other radiographic findings that may be observed are bronchiectasis in the region of the aspergilloma, an extensive area of patchy infiltrate, and lobar shrinkage contiguous to the fungus ball cavity.[82] Aspergilloma is predominantly located in the upper lobes.[45,77] A report from the British Tuberculosis Association found that the fungus ball was located in the right upper zone

in 37% of the cases, in the left upper zone in 50% of the cases, in the right middle zone in 5% of the cases, and in the left middle zone in 7% of the cases.[134] Strontium-85 uptake by soft tissue infected by *Aspergillus* during radionuclide scanning was first reported by Ray et al,[135] who believed that the *Aspergillus* metabolized and concentrated the isotope and that the strontium was bound to the fungal hyphae. Yet, as noted by Adiseshan and Oliver,[136] this was not supported by the findings in resected aspergillomas; they found more radioactivity in the chronic inflammatory tissue surrounding the fungus ball than in the fungus ball itself.[137] Rawal and Adiseshan[138] found that culture filtrates and not the fungal hyphae contained measured proportions of radioactivity and that a fungal metabolite was responsible for strontium-85 binding. It was further suggested that *Aspergillus* metabolites may diffuse into the surrounding tissue of the cavity wall, accounting for the scanning results. These reports indicate that strontium lung scanning may provide a useful adjunct to the diagnosis of aspergilloma and other forms of aspergillosis. Other investigators, however, have reported a high rate of false positives.[139]

Fig. Aspergilloma in a preexisting right upper lobe cavity. Note the crescent sign.

Immunology

Immunological techniques, including estimation of precipitating antibody to *Aspergillus* antigen, have proved to be useful diagnostic tools. Precipitating antibodies against *Aspergillus* antigen have been found in 92% to 100% of patients. The presence of precipitating antibodies in the sera of patients suffering from pulmonary aspergillosis was reported by Pepys[36] in 1959. This was followed by the demonstration of precipitating antibodies in 98% of 57 patients studied by Longbottom et al.[140] These investigators applied agar gel double diffusion and immune electrophoresis tests and graded the tested serum according to the precipitation bands formed: grade I (positive in double diffusion tests or giving a single band in immune electrophoresis), grade II (two to four bands), grade III (five to seven bands), and grade IV (eight or more bands on immune electrophoresis). Many others have confirmed the significance of antibodies to *Aspergillus* antigen.[45,87,88,91,93,96,102,107,141,142–146] A C-substance-like material, which may produce false-positive tests by reacting with C-reactive protein, has been found in some *Aspergillus* extracts; this may be eliminated by the addition of sodium citrate to the agar gel test.[147] The precipitins may become weaker, and even disappear after removal or regression of the aspergilloma.[140,142,148–150] Postsurgical follow-up, however, has shown persistence of precipitins for as long as four years. These limitations make the test inadequate for serial determinations.[82] A negative test may be due to a well-encapsulated fungus, excess circulating antigens, immunoglobulin deficiency, a fungus with poor antigenic qualities, and immunosuppressive treatment. It has been suggested that the presence of three or four serum precipitin bands may indicate the presence of aspergilloma.[36,140]

Patients with aspergilloma have a strongly positive quantitative primary binding test, which provides serial quantitative measurements following therapy.[104,151–153] They frequently have elevated serum IgG and IgA levels,[151] and antibodies to *Aspergillus* components specific to both IgG and IgM have been found, most associated with immunoglobulin class IgG.[153] Patterson et al[104] have recently demonstrated that some patients with aspergilloma may have large quantities of serum IgE, the major portion of which is not specific for *Aspergillus*.

Positive skin reactions to the protein fraction of *A fumigatus* have been described; these consist

of an immediate reaction occurring 10 to 15 minutes after the intradermal skin test (type 1) and a delayed reaction occurring 8–10 hours later (type 3).[93,154] Although allergy has not been shown to play a part in the formation of aspergilloma, 30% to 40% of patients may demonstrate immediate skin-test reactions.[134,140] Assem and Turner-Warwick[155] demonstrated IgE and IgG cytophilic antibodies in only 2 patients with aspergilloma who had symptoms of weight loss and fatigue. However, IgG precipitating antibodies in large quantities were found in all the aspergilloma patients who were investigated.[155] Hilvering et al[96] suggested that the rarity of the type 3 reaction may be due to localization of the fungus within the cavity. Johnson[77] believed that the presence of IgG cytophilic antibodies may be the underlying mechanism for the type 3 reaction. Stevens et al[156] suggested that the type 3 reaction may be responsible for exacerbating the disease in aspergilloma patients.

Cellular immunity in patients with *A fumigatus*-related lung disease was studied by Haslam et al,[157] who demonstrated only 1 patient out of 3 with aspergilloma to have significant lymphocyte transformation to five different batches of *A fumigatus* antigen. Goldstein[158] found that patients who had a negative lymphocyte transformation or intradermal skin tests had the highest levels of precipitins in the serum, and improvement in lymphocyte response in 3 out of 4 patients occurred after the aspergilloma had been resected. Forman et al,[159] who studied 4 patients with aspergilloma, found a significant lymphocyte response to *Aspergillus* antigens in 3; all of these patients had normal serum IgE levels. They concluded that T-cell and B-cell sensitization may play a role in aspergilloma; however, further investigation is necessary to establish the role of cellular immunity in aspergilloma.

Mycology

Sputum culture frequently yields the fungus in patients with aspergilloma. Culture confirmation of the fungus in the sputum depends on whether the fungus ball consists of viable or dead fungus and on the patency of the bronchus leading from the aspergilloma.[95] McCarthy and Pepys[93] demonstrated fungal mycelia under direct microscopic examination in 39% of patients; the fungus was cultured in 57% of patients, primarily in those with positive skin tests and associated allergic bronchopulmonary aspergillosis. In other series, the fungus was cultured in 55%–100% of the patients studied.[88,107,140,144] Recent reports indicate that fiberoptic bronchoscopy may significantly increase the likelihood of isolation of the fungus.[128,160,161] Sputum eosinophilia may be present in patients with an associated allergic component. Pulmonary function studies are of little help in the diagnosis of aspergilloma. McCarthy and Pepys[93] found that most patients with positive skin tests and associated allergic bronchopulmonary aspergillosis had an obstructive pattern, while some patients in these two groups and patients with negative skin tests had a restrictive pattern. The diffusing capacity was reduced in all patients. Inhalation challenge with *Aspergillus* antigen, although not routinely used, may help to distinguish those patients who are hypersensitive to *Aspergillus* and who may benefit from corticosteroid therapy.

Therapy

Treatment should be individualized for each patient. The selection of a mode of therapy should be based on the presence or absence of hemoptysis and its severity, the underlying disease, the number and size of the aspergilloma, and the presence or absence of an allergic response. Many treatment modalities have been used, but most investigators agree that, if an aspergilloma is associated with hemoptysis, cough, and sputum production, the treatment of choice is resection, provided the patient is a reasonable operative risk.[102,105,128,129,133,162] Gerstl et al[97] performed the first surgical resection for pulmonary aspergillosis. Soltanzadeh et al[163] reported 14 patients with aspergilloma, all of whom underwent surgical resection. Three of these underwent pneumonectomy, 10 underwent lobectomy, and 1 underwent segmental resection. One patient died due to congestive heart failure seven days after the pneumonectomy, and 1 had a persistent air leak following the lobectomy, which responded to prolonged thoracostomy drainage. Follow-up evaluations of 13 patients from six months to 10 years demonstrated no recurrence of the disease. Henderson et al[164] reported 24 patients with aspergillosis that underwent roentgenography; in 11 cases, a typical radiographic finding was noted (a fungal mass with air crescent), in 12 cases, the nonradiographic changes were nonspecific, and in one case, the radiograph demonstrated a bulla without evidence of aspergilloma. Of these patients,

13 underwent surgical resection because of major complications or progressive disease. The postoperative mortality was 38.5% (5 patients). Death occurred in patients who had major complications, including massive hemoptysis and infection. Of the 8 survivors, 3 underwent uncomplicated lobectomies, and 5 underwent extensive and difficult resections because of dense pulmonary adherence or direct growth of the aspergilloma through and into the chest wall. Thoracoplasty was necessary for 3 patients because of poor expansion of the residual lung. Rzepecki et al[89] collected 149 cases of aspergilloma, of which 90 patients underwent surgical resection. The operative and postoperative mortality was 4%. The late mortality was 3%. In 61 cases (62%), operative procedures included pneumonectomy, extended lobectomy, simple lobectomy, bilobectomy, and polysegmentectomy (6 patients). Postoperatively, renal failure, respiratory insufficiency, and pneumonia developed in 19 patients. In 17 cases, complications included four bronchopleural fistulas, four residual air-filled spaces, three aspergillomatous pleural empyemas, two nonspecific pleural empyemas, and isolated cases of respiratory insufficiency, long-standing pleural exudates, pulmonary edema, hemorrhage, cardiac arrest, paralysis of the diaphragm, and Horner's syndrome. The overall mortality was 7%; good results were obtained in 85%, satisfactory results in 5%, and poor results in 3%. Kilman et al[165] have reported an operative mortality of 7%. Robinson and McPherson,[166] in 1962, and Eguchi et al,[167] in 1971, noted a high incidence of bronchopleural fistula and pleural infection. These investigators regarded surgical resection as the treatment of choice. Karas et al[128] recommended surgical resection of all patients with aspergilloma, provided that they are reasonable operative risks, and noted that, because of the potential for massive hemoptysis, which may ensue suddenly, aspergilloma should be considered a life-threatening problem. Sarosi et al[168] proposed a conservative approach; however, they believed that surgical treatment was necessary in patients who subsequently have massive hemoptysis. Faulkner et al[169] reviewed their experience with 42 patients with aspergilloma, evaluated over a period of 22 years, to determine the need and advisability of surgical resection. Of these, 29 patients (69%) had sustained one or more episodes of gross hemoptysis; 11 underwent lobectomy, wedge resection, or cavernostomy. Five of these 11 patients had hemoptysis preoperatively, including 1 patient with massive bleeding. One death among the 11 patients occurred; the patient was undergoing surgery for control of massive hemoptysis. Nonoperative treatment was selected in 31 patients because of chronic lung disease; 24 of these experienced 41 episodes of gross hemoptysis during an observation period of eight years. Superimposed bacterial infection usually accompanied the episodes of hemoptysis, and medical therapy with bed rest, antibiotics, and postural drainage was successful in controlling the bleeding in 40 of the 41 episodes. One patient died of massive hemoptysis. These investigators suggested that surgical resection for pulmonary aspergilloma is indicated only in patients with massive hemorrhage, and that individuals with underlying tuberculous cavities are most likely to benefit. Surgical treatment, including lobectomy, wedge resection, or segmentectomy, has been used with success in a large number of patients with localized disease.[97,98,105,128,129,143,164,165] The operation of choice is lobectomy, but pneumonectomy and segmental resection is necessary in some cases.[49,98] The operative mortality and morbidity depends on patient selection and has been minimal with proper patient selection. The overall mortality rate in 188 reported cases of surgical resection was approximately 7%.[89,98,105] The most frequently encountered complications have been bronchopleural fistula and pleural infection.[98,164,167,170,171] Extrapleural thoracoplasty, occasionally combined with localized instillation of amphotericin B, has frequently been successful in eliminating the pleural infection.[105,165,172] A conservative approach, including medical therapy or limited surgical intervention, should be applied in patients with multiple aspergillomas. Pecora and Toll,[172] however, have advocated surgery in selected cases of bilateral aspergilloma. Saliba et al[171] suggested that presurgical treatment with amphotericin B may reduce the frequently encountered complications of bronchopleural fistula and pleural infection.

Various drugs with different routes of administration or a combination of medical and limited surgical therapy have been used to treat pulmonary aspergilloma, particularly in patients in whom the pulmonary or cardiac status has precluded surgical resection.[121] Amphotericin B alone has been shown to be ineffective for aspergilloma.[123,173] However, Reddy et al,[121] after treating 8 patients with amphotericin B, con-

cluded that this drug has a favorable influence on the course of the disease by altering the mortality. Despite these observations, treatment with amphotericin B alone has not proved helpful,[101,129,173] and according to the American Thoracic Society, amphotericin B plays no role in the treatment of aspergilloma.[174]

Henderson and Pearson[162] administered the antifungal agent, natamycin, either by inhalation or intrabronchial institution to 3 patients who then underwent evacuation of the cavity containing the aspergilloma through a small thoracotomy. This was followed by direct irrigation of the cavity with natamycin. This therapeutic approach resulted in relief of the hemoptysis and cure of the aspergilloma. These investigators stated that this approach is simple, effective, free of complications, and practicable. Ramirez[175] described a different approach in which, through a semi-permanent catheter, 1% or 2% sodium iodide and amphotericin B were instilled endobronchially; this proved effective in all 3 patients treated. Ikemoto[176] reported a similar technique in one patient. Adelson and Malcolm[83] and Aslam et al[177] used a percutaneous approach for instillation of sodium iodide and amphotericin B.

Hargis et al[178] described 6 patients with symptomatic pulmonary aspergilloma, whom they treated with percutaneous instillation of intracavitary amphotericin B. Four patients who received the full course of amphotericin B improved, 1 patient did not tolerate amphotericin B, and the other failed to respond. These investigators concluded that this mode of therapy is indicated in patients with persistent fever, weight loss, a worsening radiographic picture, repeated positive sputum cultures for *Aspergillus* and *Aspergillus* precipitins, and those who are inoperable. Cavernostomy with removal of the fungus ball, followed by thoracoplasty, has been successfully used in poor-risk surgical patients.[169] Clotrimazole has been reported to be ineffective for treatment of aspergilloma.[179,180]

Some patients with aspergilloma may have systemic symptoms, including fever, weight loss, malaise, and cough productive of large amounts of sputum.[42,93,106,127] It is believed that these symptoms are due to *Aspergillus* sensitization, and, according to Ein et al,[181] such patients may have the complete clinical picture of allergic bronchopulmonary aspergillosis. Davies and Somner[106] treated 2 such patients with corticosteroids, which produced improvement in systemic symptoms, although the aspergilloma remained. Some investigators have suggested that corticosteroids are capable of promoting fungal growth in man, and there is some risk that an aspergilloma may progress to invasive pulmonary disease.[71,90,119,182,183] Israel and Ostrow[107] observed that 7 of their patients were receiving corticosteroids before the development of aspergilloma. Because of severe dyspnea, corticosteroids were continued in 3 patients; they did not demonstrate evidence of exacerbation. The investigators concluded that it was not certain that corticosteroid therapy was responsible for aspergilloma or its progression in their patients. The prognosis of patients with aspergilloma depends on the nature and severity of the underlying disease. The treatment of an uncomplicated aspergilloma remains controversial.

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