Invasive pulmonary aspergillosis: A study of 39 cases at autopsy

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ABSTRACT

Background: *Aspergillus* is a common cause of invasive mycosis, especially in immunocompromised or immunosuppressed individuals.

Aims: To study the incidence of invasive pulmonary aspergillosis and evaluate the predisposing factors and clinico-pathological manifestations.

Settings and Design: Retrospective analysis of autopsy material from a tertiary care hospital.

Material and Methods: All autopsies performed over a 12-year period were reviewed and cases with invasive aspergillosis were analysed with respect to their clinical presentation, predisposing factors, gross and histological features, complications and causes of death.

Results: Among a total of 20475 autopsies performed in 12 years, 39 patients (0.19 %) had invasive pulmonary aspergillosis. There were 28 males and 11 females. Their ages ranged from five months to 67 years. Dyspnoea, fever, cough with mucopurulent expectoration, chest pain and haemoptysis were commonly encountered symptoms. Forty-one per cent of the patients had no respiratory symptoms. Fungal aetiology was not entertained clinically in any of the patients. The major underlying conditions were prolonged antibiotic therapy, steroid therapy, and renal transplantation, often associated with underlying lung diseases. Pneumonia, abscesses, vascular thrombosis and infarction were common findings at autopsy. Antecedent tuberculosis, mucormycosis, *Pneumocystis carinii* pneumonia and *Cytomegalovirus* infection were also present. In most cases, death was related to extensive pulmonary involvement or fungal dissemination.

Conclusion: A diagnosis of invasive pulmonary aspergillosis should always be borne in mind whenever one is dealing with recalcitrant lung infections even with subtle immunosuppression. Radiological investigations and serologic markers can be utilised for confirmation and prompt therapy.

KEY WORDS: Lung, Aspergillus infection, invasive aspergillosis, immunosuppression

Aspergillus is a common cause of invasive mycosis and the incidence is showing a rising trend following organ transplantation, chemotherapeutic modalities and other causes of immunosuppression. [1] Autopsy data have been few and have stressed the occurrence in haematological disorders, solid organ transplantation and human immunodeficiency virus (HIV) infection.[2–4] This prompted us to study the incidence of invasive pulmonary aspergillosis (IPA) with respect to the underlying causes and pathological manifestations of the *Aspergillus* invasion.

Material and Methods

This was a retrospective study, conducted in a large tertiary care general hospital that largely caters to the middle and lower socio-economic classes. There is a renal transplant program with an average of 20 to 25 live-related transplants annually; there are no specific oncology services. The incidence of HIV positivity among the admitted patients ranges from 11 to 12%. As per the hospital policy, autopsies are not performed in such patients. The autopsy rate is about 20%. All autopsies performed over a period of 12 years were reviewed and those cases indexed as IPA were analysed. The relevant clinical data was obtained from indoor case sheets in the medical records department, and autopsy records kept in the pathology department. Age, gender, duration of admission, predisposing factors, clinical features, investigations, gross and microscopic features in the lungs and other organs, complications and causes of death were noted. Relevant sections were retrieved and reviewed. All sections were stained with haematoxylin and eosin. Gomori's methenamine silver was the special stain used to identify the fungal elements.

Results

Among a total of 20475 autopsies conducted over 12 years, there were 39 patients with IPA (0.19%), affecting 28 males and 11 females. Their ages ranged from five months to 67 years. Males in the second and third decades of life were commonly affected. Patients were admitted for a period of 15 hours to 33 days. Less than half of the patients were admitted in the intensive respiratory care unit; others were from general medical units with a few from surgical specialities. The chief symptoms were fever, breathlessness, cough with or without mu-

copurulent sputum, chest pain or haemoptysis. Two patients developed the above symptoms during their stay in the hospital. Sixteen patients (41%) did not have respiratory symptoms.

The main predisposing factors were prolonged antibiotic therapy, steroid therapy and renal transplantation (Table 1) . Twelve (30.8%) had more than one predisposing factor. Six were in intensive care units for ten or more days, some requiring ventilatory care. Six had no apparent predisposing factor.

Haematological findings were not available in 11 patients. The remaining had anaemia (14), neutrophilia (15), eosinophilia (1), atypical lymphocytosis (1), neutropenia (1), pancytopenia (2) and normal leucocyte counts (6). Chest radiography revealed bronchiectasis in two, unilateral or bilateral opacities in nine, fluffy shadows and cavitary lesions in two cases each and reticulo-nodular shadows in one. Radiological features could not be reviewed in the remaining 22 patients. Fungal aetiology was not suspected clinically in any of these patients. Sputum was positive for *Aspergillus* species in two patients where sputum and bronchial secretions were sent for routine cytological examination. These were submitted for culture studies. Acid-fast bacilli or *Pneumocystis carinii* were present in two others. Serology was positive for leptospirosis in two and for *Cytomegalovirus* in one.

On gross examination of lungs, 17 cases showed patchy to diffuse pleural fibrosis. Film of fibrinous or fibrinopurulent exudate over the visceral pleura was present in 15. Barring four cases, the lungs revealed greyish white to yellow areas of pneumonic consolidation. These were bilateral and multifocal in all except 1 case, where it was restricted to the right upper lobe. Alveoli were filled with polymorphonuclear inflammatory exudate, with break down of the alveolar septa and formation of abscesses (27 cases). The fungal colonies often tended to be confined to the necrotic material and appeared as branching, slender, septate hyphae (Figure 1). Gross cavitations were noted in 15 patients that contained grey white semisolid contents.

Another characteristic noted in many lungs was angioinvasion (28 patients), producing bland thrombi (19 cases) and/or acute necrotising arteritis (6 cases, Figure 2). This resulted in two distinct pathologic variants. Twenty-four patients showed subpleural, wedge-shaped foci of haemorrhagic infarction or areas of haemorrhage. In addition, seven patients also showed the so-called target lesions (Figure 3). These appeared as fairly well-circumscribed, non-subpleural lesions with pale centres

Table 1: Predisposing factors in invasive pulmonary aspergillosis (N=39)

Factor	Number of cases
Steroid therapy	09
Prolonged antibiotic therapy	08
Pulmonary tuberculosis	11
Bronchial asthma	06
Renal transplant	04
Chronic obstructive pulmonary disease	03
Pancytopenia	03
Malaria	02
Rheumatoid arthritis	02
Leprosy	01
No predisposition	06

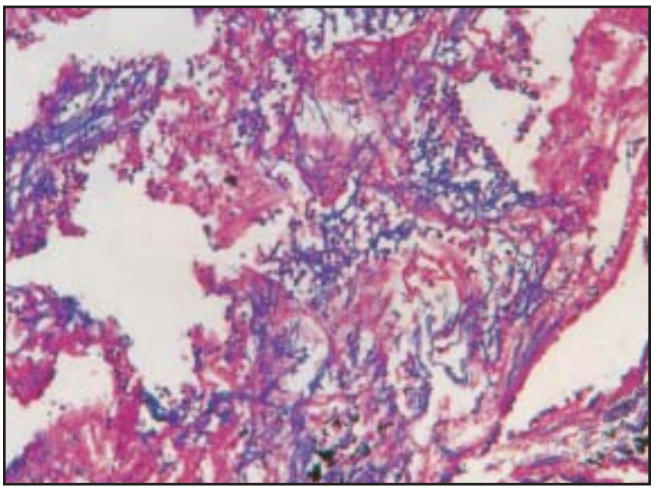

Figure 1: Necrotic parenchyma, invaded by basophilic delicate branching *Aspergillus* hyphae

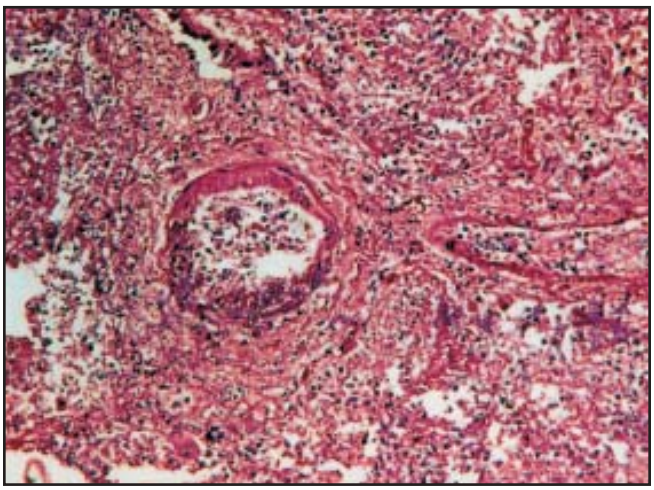

Figure 2: Necrotising arteritis and parenchymal inflammation

Figure 3: Target lesions, composed of pale necrotic areas with haemorrhagic rims

Figure 4: Main bronchi occluded by coagulated exudate. Note shaggy appearance of the tracheal mucosa

Figure 5: Granulomatous aspergillosis, prominent thickening of the bronchovascular bundles and miliary areas

and haemorrhagic borders. The pale areas were composed of coagulative necroses of the lung parenchyma with a tangle of fungal hyphae. Inflammatory reaction was significantly absent. These were bordered by congested or haemorrhagic viable parenchyma. This was the sole finding in one case, a young male operated for rheumatic heart disease with postoperative mediastinitis.

Involvement of the tracheobronchial tree was seen in six patients. Two among these were not associated with pneumonia. One had acute necrotising bronchiolitis. The other, a case of leptospirois on mechanical ventilation, had obliterative shaggy yellowish brown exudate in the bronchi with ulcerative tracheitis (Figure 4) along with lung infarction. One other case had unusual findings. The patient, a 17-year-old male had paroxysmal episodes of breathlessness since childhood with streaky haemoptysis. The patient had been treated with anti-tuberculous drugs and steroids in the past, with no response to therapy. Diagnostic bronchoscopy was performed. Secretions were aspirated and transbronchial lung biopsy was performed. Septate hyphae were seen in the bronchial secretions. Biopsy showed granulomatous inflammation, in which hyphae could be demonstrated within the giant cells. This was the only patient who received anti-fungal therapy, but expired within 24 hours of the institution of specific therapy. On gross examination, pleurae were markedly thickened with multiple yellow nodules fused to form geographic areas. Cut surfaces revealed accentuation of the lobular septa and bronchovascular bundles with nodular and miliary areas (Figure 5). Mediastinal lymph nodes were enlarged and had similar firm yellowish appearance. On microscopy, multiple granulomata (Figure 6) were seen with colonies of fungal hyphae, involving the airways, parenchyma and vessels and the lymph nodes, an example of granulomatous aspergillosis.

Fibrocavitary tuberculosis was seen in five with aspergilloma and post-tuberculous bronchiectasis in two cases each. Active tuberculosis was present in six. Additional organisms detected in the lung sections were *Candida* (1 case), *Mucor* (2 cases), *Pneumocystis carinii* (2 cases) and *Cytomegalovirus* (1 case).

Apart from the lungs, other organs also bore the brunt of the aspergillus onslaught in eight patients (20%, Table 2). The chief finding was suppurative cerebritis (62.5%). In addition, multi-

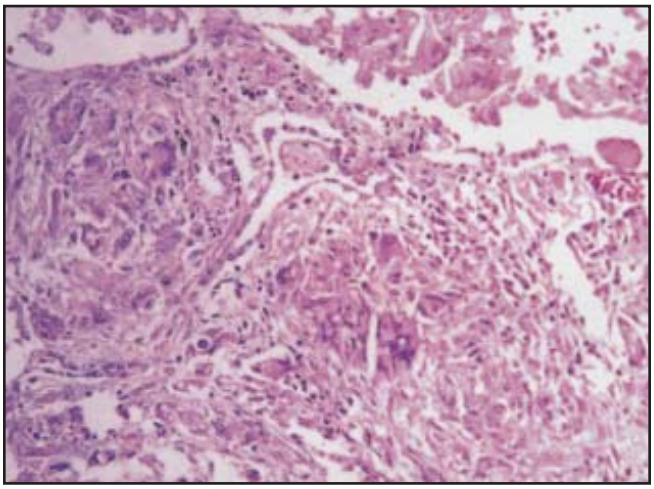

Figure 6: Non-caseating granulomata with lung destruction

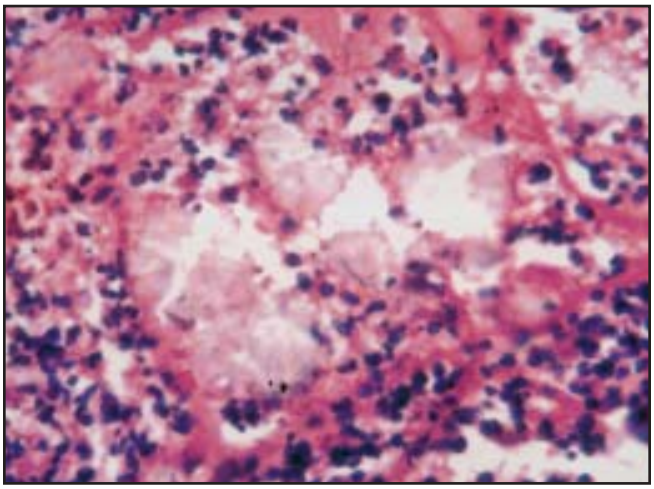

Figure 7: Irregular, pale staining. refractile calcium oxalate crystals

Table 2: Extra pulmonary involvement in invasive pulmonary aspergillosis (N=39)

Extrapulmonary manifestation	Number of cases
Suppurative cerebritis	05
Renal infarction / abscesses	03
Myocarditis	02
Oesophagitis	01
Gastritis	01
Pancreatitis	01
Hepatic abscess	01
Splenic abscess	01
Peritonitis	01

Table 3: Causes of death in invasive pulmonary aspergillosis (N=39)

Cause	Number of cases
Respiratory failure	18
Disseminated aspergillosis	03
Raised intracranial pressure	04
Renal failure	04
Septicaemia	02
Bacterial infective endocarditis	02
Perforative peritonitis	02
Leptospirosis	01
Chronic malaria	01
Disseminated tuberculosis	01
Non-specific aortoarteritis and mulitorgan infarction	01

organ zygomycosis involving the cerebral hemispheres, transplanted kidney and stomach was seen in three patients. In the majority (46.1%), mortality was related to extensive lung involvement (Table 3). Calcium oxalate crystals were identified as irregularly angulated, polarizable material amidst inflamed and necrotic lung parenchyma in three cases (Figure 7). Interestingly, acute renal failure in two patients was due to oxalate crystals plugging the renal tubules.

Discussion

The ubiquity of the fungus *Aspergillus* is a major factor in designating our planet as 'our mouldy earth'. The fungus *Aspergillus* was baptized by the priest and botanist Micheli in 1729 since it bore resemblance to the perforated globe used for sprinkling holy water.[5] But the effect of the fungus is far from holy. Although the fungus can colonize any organ, the lungs are the most commonly affected. Depending on the host immunity, lung structure and degree of inoculum, pulmonary aspergillosis is classified into three types; Allergic, with a characteristic hypersensitivity reaction to the fungal elements, Saprophytic in which there is fungal colonisation of airways or parenchyma ('Fungal ball' formation), devoid of destruction of viable tissue, or Invasive where the fungus evokes necrotizing suppurative or non-suppurative parenchymal lesions.[1, 6-8]

Invasive aspergillosis has acquired great importance as a cause of much morbidity and mortality in immunocompromised or immunosuppressed patients.[1] Though there are probably about 180 species of *Aspergillus*, only a handful cause human disease, especially A. *fumigatus*, rarely A. *niger* and a few others. A diagnosis of IPA requires repeated isolation of the fungus from the airways with appropriate clinical or radiological features and/or positive tissue diagnosis. These are identified as regular slender, septate hyphae that branch dichotomously at an angle of 45 degrees, a pattern closely mimicked by other genera like *Pseudoallescheria* or *Fusarium*.[1] In our study, since the organisms were not cultured in any, we have presumed Aspergillus aetiology in all on the basis of mere morphology.

Impairment of host defence, either overt or covert, is essential for the development of IPA. Central to this is an impairment or deficiency of phagocyte function (granulocytes or tissue macrophages).[9] Hence patients with haematological disorders like acute leukaemias and aplastic anaemias are particularly prone to this complication.[10] Patients with non-haematological malignancies[11] or with organ transplantation[5] are also similarly afflicted. In the present series, we had three cases of pancytopenia. Surprisingly, none of the 81 cases of leukaemia or lymphoma encountered at autopsy had evidence of pulmonary aspergillosis. There were four cases with renal transplant.

The main predisposing factors in this study were prolonged antibiotic therapy, steroid therapy and alteration of pulmonary architecture or local immunity such as bronchial asthma, tuberculosis or chronic obstructive pulmonary disease. Such factors have been implicated in the causation of semi-invasive or chronic necrotising aspergillosis, initially described in the 1980s.[12,13] This results in a cavitary lesion, especially in the upper lobes, with surrounding acute or chronic inflammation with or without fungal ball formation.[14] This variety supports the concept that the allergic, saprophytic and invasive forms may represent a spectrum of disease dependent on lung structure and immune status.[12] All our cases had the morphology of the usual acute invasive form. Only one patient had disease restricted to the right upper lobe but did not have the aforementioned characteristics of the semi-invasive form. Aspergilloma were present in two cases with fibrocavitary tuberculosis, with subsequent invasion as occurs with the saprophytic variant.[1]

Diabetes mellitus, alcohol abuse, renal or hepatic failure which affect neutrophil proliferation, maturation, function and lifespan, and other immunological disorders are other predisposing factors.[1,12,13] These represented a small proportion in our patients. Despite a primary T cell dysfunction in HIV infection, these patients are prone to IPA, probably as a result of other common predisposing factors.[15,16] We have not come across any case of AIDS in our study. In general, autopsies are not performed in established cases of AIDS at our institution. Fungally contaminated aerosol due to defective disposal or environmental manipulation such as hospital reconstruction projects can lead to an outbreak of IPA.[17,18] Maximum number of cases were seen by us in 1996 (11 cases) but unrelated to the above mechanisms. Similarly, prolonged stay in intensive care units and / or mechanical ventilation has also been implicated.[19] Seven of our patients had such a history. Six other patients did not have any apparent predisposition, including to extreme exposure to *Aspergillus* spores, as occurs at times.[20,21] On the whole, it appears that majority of patients in this autopsy series, were not greatly immunocompromised. Also, this rate of

aspergillosis (0.19%) may not represent the true incidence in a general hospital setting, since all the fatal cases of IPA and the known HIV positive cases are not autopsied. Furthermore, fungal stains were not routinely performed in all cases of consolidation, abscesses or infarction and therefore gross disease was probably picked up but not the minor disease. Nevertheless, it is quite different from the autopsy series, where majority of the patients have had solid organ transplantation or haematological disorders, especially leukaemais.[2-4,22]

Most patients had respiratory symptoms, clinical signs, laboratory and radiological features no different from bacterial pneumonias. Hence a diagnosis of IPA was not made clinically in any of these patients. A high index of suspicion is therefore very essential, especially in immune depleted cases. Fine needle aspiration cytology or biopsy can be done to demonstrate fungal hyphae destroying viable tissue.[23] Alternatively, galactomannan antigen or DNA detection may be adopted for early diagnosis and management.[24, 25] Many of these tests have been recently developed and if now employed would ensure high pick-up rate. However, difficulties arise when there are no respiratory symptoms as seen in 43 % of our patients.

IPA manifests as several distinct clinicopathological forms, namely acute bronchopneumonia, angioinvasive aspergillosis, acute tracheobronchitis, miliary aspergillosis and pleural aspergillosis.[1] Despite this classification into various morphologic subtypes, we found a combination of lesions in most. The commonest finding was the presence of multifocal consolidation, complicated by abscess formation. Central cavitation with shaggy walls and semisolid gray white contents was an additional feature. This occurred in 4-16%, caused by the separation of the infected portion from viable parenchyma.[11] Separation and dissolution occurs due to enzymes released from neutrophils or *Aspergillus* species.[11] The former plays a more important role as documented by Albeda et al [26] where cavitation coincided with recovery from neutropenia. This may at times aid in the radiological diagnosis of the disease [27,28] with a characteristic crescent or halo sign. But in other cases, the appearance is no different from bacterial consolidations.[28] Later in the course of the disease, these cavities instigate formation of fungal balls.[29] We did not record any such phenomenon. Aspergilloma in this study occurred in tuberculous cavities.

Angioinvasion was the next common manifestation, and accompanied bronchopneumonia in 26. This produces bland thrombosis and/or vasculitis and subsequent infarction. The other variant of angioinvasion, target lesions, were present in seven. These are said to represent coagulative necroses of the lung due to enzymes or toxins elaborated by the fungi. Pure angioinvasive disease was seen in only one patient. Pleural thickening and fibrosis as noted in a few of the cases were most commonly due to tuberculosis. In the other cases, though there was an inflammatory exudate, fungal hyphae were not demonstrated. Aspergillous tracheobronchitis is a rare and often sole manifestation with pseudo-membranes partly or completely occluding the airway lumina.[30-32] This can involve the airways at all levels. We had five such cases, one of which had only acute bronchiolitis. There was no case of miliary aspergillosis. We came across an interesting case of granulomatous aspergillosis,[33] not well documented in literature. He was a 17-year-old male with a history of bronchial asthma (possibly allergic broncho-pulmonary aspergillosis) with blood and sputum eosinophilia. Non-caseating granulomata systematically destroyed the pleura and the pulmonary interstitium. This is an example of the allergic form paving the way for true invasive aspergillosis.

Certain *Aspergillus* species, particularly *A. niger* are associated with the production of oxalic acid, through tricarboxylic acid cycle. The oxalic acid so generated combines with the host-derived calcium to form birefringent calcium oxalate crystals. Thus demonstration of these crystals in tissue or fluid indicates some type of fungal infection.[34] Crystals were identified in three patients, two of whom developed acute renal failure following renal hyperoxalosis.

IPA is a devastating disease. Since the manifestations vary according to the immune status of the host and the underlying lung disease, the clinical and radiographic features vary.[35] Therefore, it should always be considered in the differential diagnosis of pneumonia, tuberculosis, lung abscess and bronchiectasis.[36] Despite early diagnosis, the disease is difficult to treat because of extensive pulmonary involvement and /or extra pulmonary dissemination. Twenty percent of patients had extra pulmonary involvement. Besides, coexistent infections that flourish in immunodeficient background, as seen in 30.7 % of patients in this study, add to the mortality and morbidity.

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