ACUTE ASPERGILLUS BRONCHO-PNEUMONIA REPORT OF A CASE

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Pulmonary aspergillosis, primarily a disease of birds, is a relatively rare infection in man. Review of the literature reveals numerous case records of aspergillus infections as secondary complications of other primary lung diseases; (Heppleston and Gloyne, 1949; Hinson, et al, 1952; Zimmerman, 1955; Utz, J.P. et al, 1959; Gowing and Hamlin, 1960; and Villar, et al, 1962). The three cases of Pulmonary Aspergillosis described by Virchow in 1856 (quoted by Boyce, 1893) are the first carefully studied cases and are probably the earliest to show that aspergillosis manifests itself as a primary pulmonary disease. Boyce (1893) while giving a detailed account of the first case of Primary Aspergillosis reported in England, concluded that the Aspergilli in man do not seem to be severely pathogenic. Primary pulmonary aspergillosis is still a rare disease in man, the majority of reported cases are either complicating Hodgkin's disease and Leukaemia, (Gowing and Hamlin, 1960) or associated with the use of multiple antibiotics, steroids and hormones (Abbott, et al, 1952, Zimmermam, 1955; and Spencer, 1962). Most of the cases of the primary disease presented with Chronic granulomas and it is only in a few instances that an *acute* pneumonic reaction was described (Delikat, 1945; Cooper, 1946; and Ross, 1951).

The following case of *acute* primary pulmonary aspergillosis seems to be the first of its kind in the autopsy records of Singapore.

CASE REPORT

Y.K.L., a 49 year old Chinese female was admitted to the General Hospital on 5th. May 1962 with 10 days history of pain in the epigastrium. The epigastric pain was aggravated by taking food and relieved with rest.

Clinical examination revealed deep jaundice. The lungs and heart showed no abnormalities. Patient's temperature was within normal limits until towards the end when it rose to 101°F.

Chest X-rays were clear at the time of admission. Laboratory findings showed:— Serum bilirubin 11 mgm.% which rose to 23 mgm.% a day before death; Hb: 83%; W.B.C.: 8,000/cmm.—90% neutrophils, 6% lymphocytes. 4% monocytes and 0% eosinophils.

Treatment was started on the 8th. of May and consisted of Achromycin 250 mgm. 6 hourly and Prednisolone 45 mgm. daily. While still on the antibiotic and steroid therapy, the patient died on the 30th. of May 1962.

NECROPSY FINDINGS (No. 1123/62)

The body was that of a well built, deeply jaundiced Chinese female of about 49 years of age. The peritoneal cavity contained about 3500 ml. of bile stained fluid. The liver was shrunken. weighed 700 grams. and had nodular outline. The major findings to account for the clinical picture were those of monolobular liver cirrhosis and liver failure.

No further details of post-mortem findings will be included other than those of the lungs. The pulmonary disease, although not diagnosed or suspected during life, constitutes the subject matter of this paper.

GROSS APPEARANCE OF LUNGS

Both lungs showed multiple consolidated nodules in all lobes, some of the nodules were subpleurally situated. On section, the nodules were moderately firm, greyish and surrounded by hyperaemic zone of crepitant lung tissue.

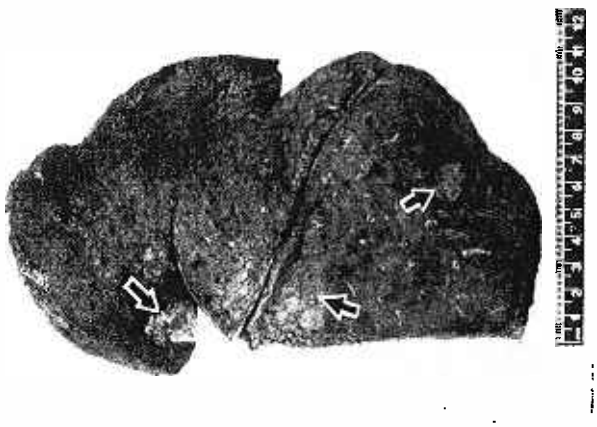

Fig. 1. Cut surface of the right lung showing three pneumonic nodules. Note the hyperaemic zone surrounding the areas of consolidation.

The appearance vaguely resembled that of metastatic tumour nodules (Fig. 1). However, the nodules, the largest of which measured about 3.5 cm. in diameter, were not clearly demarca-

ted from the surrounding lung tissues and when squeezed found to contain inspissated purulent exudate.

HISTOLOGICAL OBSERVATIONS (LUNG SECTIONS)

Paraffin sections taken from various areas of both lungs and stained with Haemotoxylin and Eosin show confluent areas of bronchopneumonia. There is peribronchial consolidation and the alveoli in the areas of consolidation are filled with fibrino-purulent exudate rich in polymorphonuclear cells and a few scattered macrophage cells. The bronchial and bronchiolar epithelium is destroyed and in places heavily infiltrated with polymorph leucocytes. There is a zone of vascular stasis in the periphery of the consolidated pneumonic nodules but no thrombi are seen in any of the sections. The alveolar walls are mostly necrotic and amongst the cell debris there are collections of faintly basophilic, translucent, poorly outlined fungal hyphae (Figs. 2 a & b). The hyphae, averaging about 5 microns in diameter, show branching and club-shaped expansions but no spores are visible.

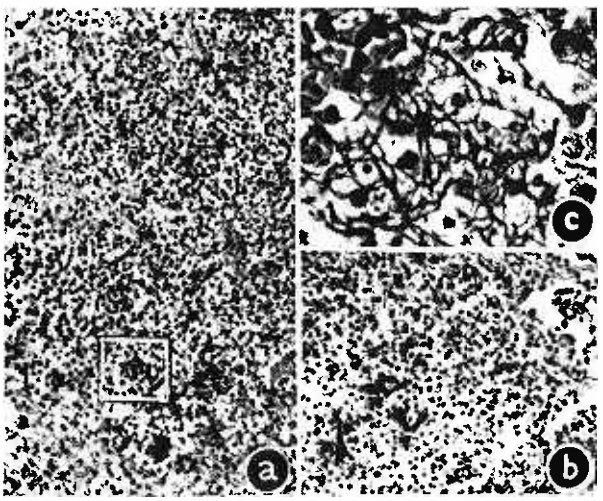

Fig. 2. (a) Section of the lung showing acute inflammatory exudate in alveolar spaces. H & E x 150.

(b) A low power appearance of fungal hyphae in the middle of the alveolus and surrounded by acute inflammatory cells. H & E x 150.

(c) High power view of the boxed area in figure 2(a) showing fibrinous exudate. Fibrin coloured deep blue in original preparation: black in photograph. P.T.A.H. stain x 500.

Several selected sections were stained with special staining techniques for fungi i.e. Periodic-acid-Schiff technique (P.A.S.) and Gomori's Silver Methenamine stain (G.S.M.). Other sections were stained with Phosphotungstic Acid-Haematoxylin (P.T.A.H.) to demonstrate the fibrinous exudate in the alveoli (Fig. 2c). Although the fungal hyphae were well demonstrated with the P.A.S. stain, the best results were obtained with the Silver stain (G.S.M.); hyphae not visible by other methods and branching are well defined (Fig. 3).

Detailed histological examination and special staining showed no disseminated fungal lesions in other organs.

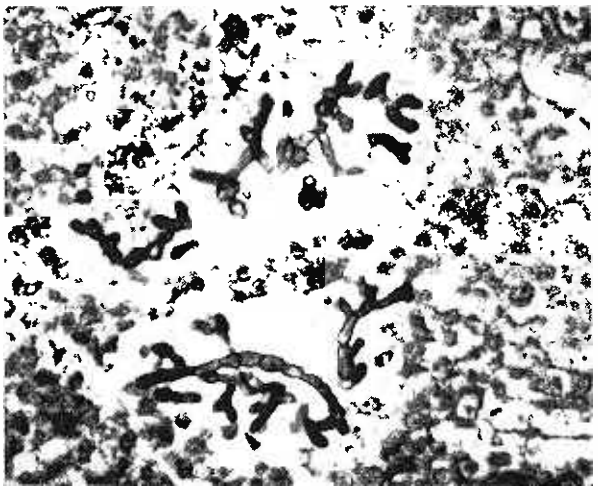

Fig. 3. Silver Staining showing the clarity with which fungal hyphae can be seen in tissue sections. G.S.M. stain x 500.

MYCOLOGICAL STUDY

Pieces of the lung nodules were collected in sterile tubes and cultured for fungi. The tissue was minced and then inoculated into several

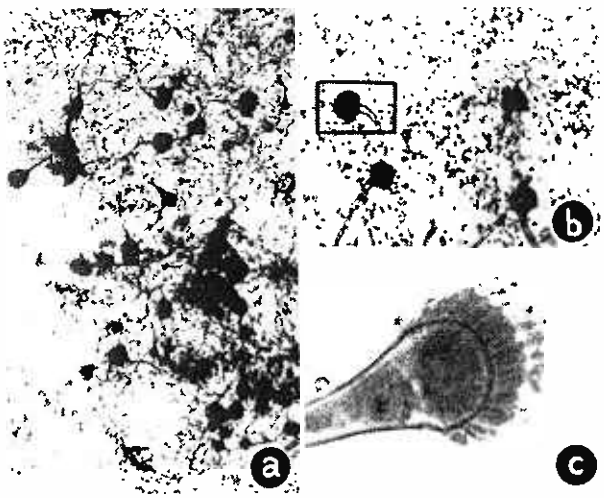

Fig. 4. Smear (*Aspergillus fumigatus*) taken from the growth on Sabouraud's Medium and stained with Lactophenol cotton blue.

(a) Mycelium of hyphae and conidiophores.

(b) Mycelium and spores.

(c) Enlarged conidiophore (note the resemblance to the shape of Aspergillum).

The morphological structure is diagnostic of A. fumigatus x 500.

glucose Sabouraud's Media containing penicillin and streptomycin. Incubation at room temperature for five days yielded pure growth of *Aspergillus fumigatus* which were identified by Mrs. B. Stein, M.Sc. (Fig. 4 a, b & c).

DISCUSSION

Aspergillus, a fungus included in the class Ascomycetes and the genus *Aspergillus Micheli* (the name having been adopted by Micheli in 1729 (Ross, 1951). Aspergilli are inhabitants of the soil and decaying organic matter. The fungus received its name from the shape of the fruiting head which resembles the brush used for sprinkling Holy Water known as "Aspergillum" (Spencer, 1962)—see Fig. 4c. Although numerous early workers disputed Aspergilli as a cause of primary disease, Boyce (1893) found Aspergillus fumigatus as the sole causative agent in his reported case. Since then, there is mounting evidence that A. fumigatus is responsible for epizootic aspergillosis in its primary and secondary forms. However, other aspergilli were reported as the sole infective agents, namely: A. niger reported by Utz (1959). A. flavus and A. sydowi reported by Naji (1959). There is experimental evidence that Aspergillus fumigatus inoculated intratracheally into rabbits resulted in Aspergillus Broncho-pneumonia similar to that seen in human cases (Cooper, 1946). When a suspension of the fungi was injected intravenously in experimental animals, tuberculoid lesions developed in many organs including the lungs, liver, spleen, kidneys, muscle, intestines and the bone marrow (Ross, 1951). Aspergillus infections of the lungs are likely to become rapidly progressive and disseminate to other organs of the body as seen in five recently reported cases by Gowing and Hamlin (1960).

Conditions under which pulmonary aspergillosis arise, apart from the secondary infestation complicating tuberculosis, bronchoiectasis and other lung infections (Villar, et al, 1962; and Spencer, 1962), are still being investigated. So far, it is acceptable to think of aspergillosis in two main forms; those existing as secondary complication of pulmonary disease in the form of *saprophytic* infestations and the other variety of *non-saphrophytic* existence representing a form of true primary infections of the lungs and, occasionally, other organs. There are some variations in the pathological appearance of the secondary aspergillosis reported by many earlier and recent workers. However, the appearance of the so-called Aspergillus Mycetoma of the lung (Riddell, 1958) seem to adequately illustrate the tumorous mass so produced and confirmed by the recent observations of Villar, et al, (1962).

Reference has already been made to the excellent investigation presented by Gowing and Hamlin (1960) to show that aspergillosis arises as a terminal complication of lymphomas. A proportion of the cases of primary pulmonary aspergillosis might be attributed to lymphomas as a predisposing factor. Other associated or predisposing causes, particularly those connected with antibiotics and steroids, are in fact proven factors and apply to other fungal infections as well (Anderson, 1958; and Spencer, 1962). Some cases of primary pulmonary aspergillosis were considered as occupational diseases in agricultural workers, bird feeders and even in coal miners (Coe, 1945; Heppleston and Gloyne, 1949). The case reported by Coe (1945) of a 47 year old male whose work brought him in contact with animals and heavy concentration of dust, was accepted as a genuine occupational disease and declared compensable under the laws of Illinois, U.S.A.

The lesions resulting from the primary pulmonary aspergillosis are classified in three histological varieties:—

(i) *Non-suppurative Aspergillosis:*

Lesions showing cell necrosis, resembling an infarct, but show little evidence of inflammatory cell response. Gowing and Hamlin (1960) designated this type of reaction as "spreading-necrotizing".

(ii) *Suppurative Pneumonic Pulmonary Aspergillosis:*

Histological appearance of these lesions resembles that of acute forms of pneumonia (Cooper, 1946; Bech, 1961). There are often abscesses similar to bacterial pyaemic abscesses and fungi are easily identifiable.

(iii) *Tuberculoid Pulmonary Aspergillosis:*

Granulomatous reaction resembling tubercles and is usually a chronic form of the disease. This chronic form of Aspergillosis was adequately described in the earliest cases reported in the literature (Boyce, 1893). Spencer (1962) regards this reaction as a form of hypersensitivity to the fungus similar to that of tuberculous infections.

Bronchopulmonary aspergillosis occasionally manifests itself by an allergic phenomenon presenting with eosinophilia and deposits of Charcot-Leyden Crystals in the pneumonic areas (Hinson, et al, 1952). However, it is not

possible to include this form of reaction with the former three because of the lack of supportive literature on the subject. The case reported by Delikat (1945) in which she showed that the patient developed immunological response observed by testing the patient's serum against an extract of fungi, was based on clinical findings only and therefore the tissue changes were not known.

The case of aspergillosis described in this paper satisfies all the criteria for the diagnosis of *acute* primary aspergillus broncho-pneumonia. According to Pierce (1958), nearly all types of aspergillus infections of the lungs are detectable radiologically in the form of pneumonic patches or shadows, although not diagnostic, are constantly observed. X-ray examination in this case showed no abnormal shadows at the time of admission to the hospital. It is most likely that the infection developed and took an acute course during the 25 days of hospitalization. Moreover, during that same period, Achromycin and Prednisolone were continually administered. The post-mortem findings showed acute pneumonic consolidation and there were no allergic manifestations as judged by the normal eosinophilic count and the absence of characteristic tissue changes.

SUMMARY

A case report of an acute form of Aspergillus Broncho-pneumonia incidentally discovered at autopsy in a Chinese female of 49 who developed liver failure as a result of advanced cirrhosis. The infection, caused by Aspergillus fumigatus, developed in association with the combined use of Achromycin and Prednisolone. The literature on the subject of pulmonary aspergillosis has been briefly reviewed and the recent histological classification adopted.

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REFERENCES

Abbott, J.D., et al. (1952) Pulmonary Aspergillosis following post-influenzal Broncho-pneumonia treated with antibiotics. Brit. M.J. *1*:523.

Anderson, T. (1958) In Fungus Diseases and their Treatment, Edited by Riddel and Stewart. 1st. Ed., 84, London: Butterworth and Co., Ltd.

Bech, A.O. (1961) Diffuse Broncho-pulmonary Aspergillosis. Thorax, *16*:144.

Boyce, R. (1892-93) Remarks Upon a Case of Aspergillar Pneumonomycosis. J. Path. & Bact., *1*:163.

Coe, G.C. (1945) Primary Bronchopulmonary Aspergillosis an Occupational Disease. Ann. Int. Med.. *23*:423.

Cooper, N.S. (1946) Acute Broncho-pneumonia due to Aspergillus fumigatus fresenius. Arch. Path. (Chicago), *42*:644.

Delikat, E. (1945) Acute pulmonary Mycosis—Report of a case. Lancet, *ii*:370.

Gowing, N.F.C., and Hamlin, Iris M.E. (1960) Tissue Reactions to Aspergillus in cases of Hodgkin's Disease and Leukaemia. J. Clin. Path., *13*:396.

Heppleston, A.G. and Gloyne, S.R. (1949) Pulmonary Aspergillosis in coal workers. Thorax, *4*:168.

Hinson, K.F.W., Moon, A.J. and Plummer, N.S. (1952) Broncho-pulmonary Aspergillosis. A review and report of eight new cases. Thorax, *7*:317.

Hinson, K.F.W. (1958) In Fungus Diseases and their Treatment, Edited by Riddell and Stewart, 1st. Ed., 123. London: Butterworth and Co., Ltd.

Naji, A.F. (1959) Broncho-pulmonary Aspergillosis. A.M.A. Arch. Path., *68*:282.

Pierce, J.W. (1958) In Fungus Diseases and their Treatment, Edited by Riddell and Stewart. 1st. Ed.. 172. London: Butterworth and Co.. Ltd.

Riddell, R.W. (1958) Fungus Diseases and their Treatment. 1st. Ed., 22. London: Butterworth and Co., Ltd.

Ross, C.F. (1951) A case of Pulmonary Aspergillosis. J. Path. & Bact., *63*:409.

Spencer, H. (1962) Pathology of the Lung. 1st. Ed., 206. London: Pergamon Press Ltd.

Utz, J.P., et al. (1959) Pulmonary Aspergillosis with Cavitation. New Engl. J. Med., *260*:264.

Villar, T.G., Cortez Pimental, J., and Freitas, E. Costa, M. (1962) The tumour-like forms of Aspergillosis of the lung (Pulmonary Aspergilloma). Thorax, *17*:22.

Zimmerman, L.E. (1955) Fatal fungus infections complicating other diseases. Am. J. Clin. Path., *25*:46.