PULMONARY CRYPTOCOCCOSIS

W Y Cheong, A Thomas, K P Tan

SYNOPSIS

The commonest radiologic presentation of pulmonary cryptococcosis is a coin lesion. Cryptococcosis is often not considered as a differential diagnosis when other forms of presentation are encountered. The disease is uncommon locally but when an unusual pulmonary infection or tumour - like lesion is present, the possibility of pulmonary cryptococcosis should be borne in mind. This report includes five histologically proven cases of cryptococcosis, three of whom were diagnosed by percutaneous lung aspiration.

SING MED J. 1988; 29:223–231

CASE REPORTS:

Patient 1, a thirty-three year old male, was completely asymptomatic. His profession as a diver required him to have an annual chest radiograph routinely. During one such exercise in 1985, it was noted that he had an opacity in the right middle zone and was referred to Department of Tuberculous Control, Tan Tock Seng Hospital. On closer inspection, there were in fact several nodules in the right middle and upper zones (Fig. 1A). A

Illustrations — Patient 1

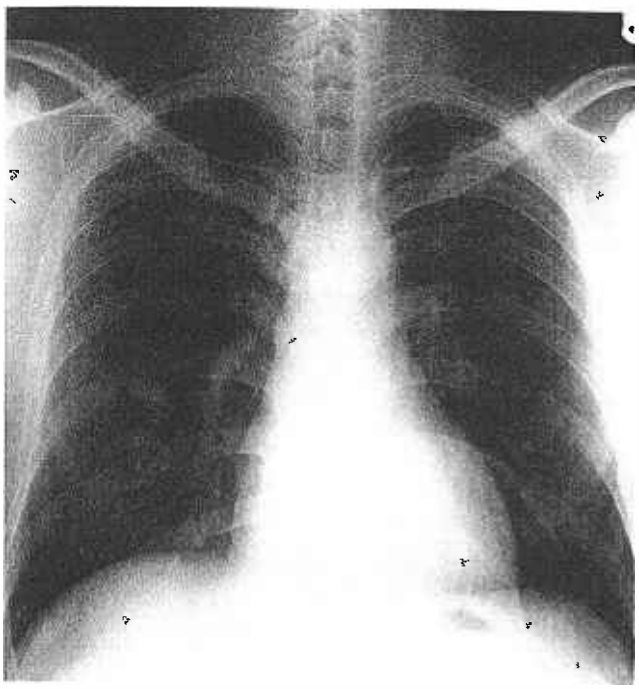

Fig. 1A

Department of Radiology
Tan Tock Seng Hospital

W Y Cheong, FRCR(UK),Registrar

Department of Pathology
Outram Road
Singapore

A Thomas. FRCPA, Senior Registrar

Department of Radiology
Tan Tock Seng Hospital

K P Tan, DMRD (UK), MRCP (UK), FRCR (UK)
Senior Radiologist and Head

Figs 1A & B. PA and lateral CXR showing multiple nodules in the superior segment of the right lower lobe and the apical segment of the right upper lobe.

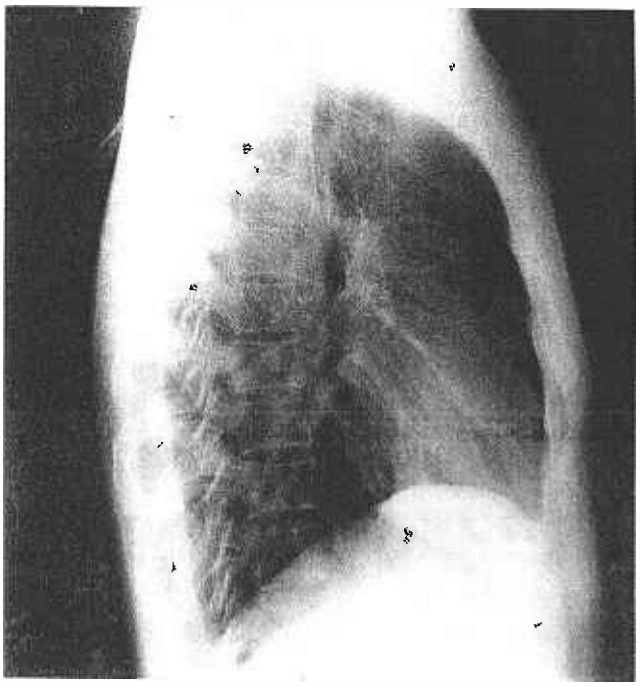

Fig. 1B

lateral radiograph placed the lesions in the superior segment of the right lower lobe and the apical segment of the right upper lobe (Fig. 1B). Tomography showed the lesions to be smooth and well circumscribed with no surrounding reaction. There was no calcification, cavitation or abnormal vasculature. The hilar nodes were not enlarged. There was no history of pulmonary tuberculosis or of exposure to it. The physical examination was normal. Based on the radiologic appearance (the benign nature, the multiplicity of the lesions and their locations), a positive Mantoux reaction of 14mm and the prevalence of tuberculosis locally, a diagnosis of multiple tuberculomata was made despite negative direct sputum smears for acid-fast bacilli and anti- tuberculous treatment was started. A chest radiograph one month later showed some improvement. However, at six months a new lesion appeared in the left upper zone despite patient compliance with therapy. The lesions in the right lung field remained unchanged after the initial response. Because of the unusual course of the disease, the patient was closely followed up despite an adequate course of treatment. In February 1986, four months after completion of treatment, the lesions in the right lower lobe had not only increased in size but the

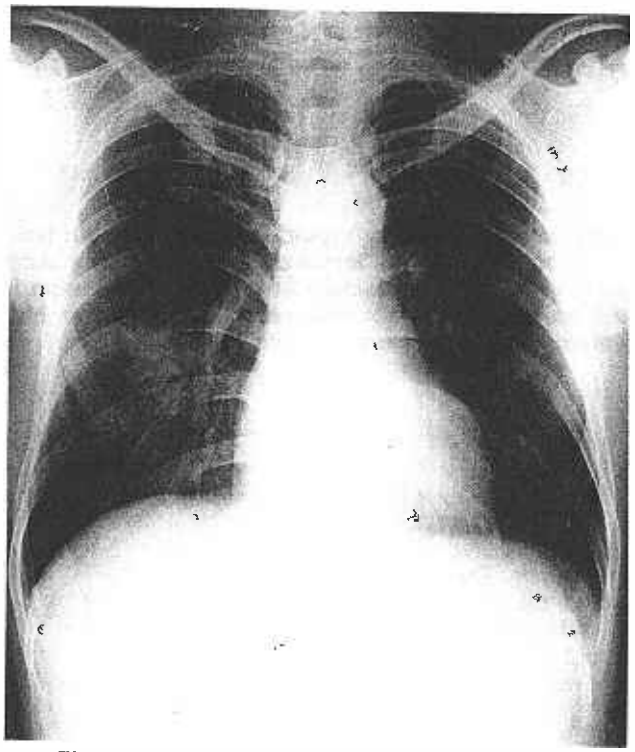

Fig 1C. Four months after anti-TB treatment. The lesions in the right lower lobe resembled an a-v malformation and that in the right upper lobe had increased in size.

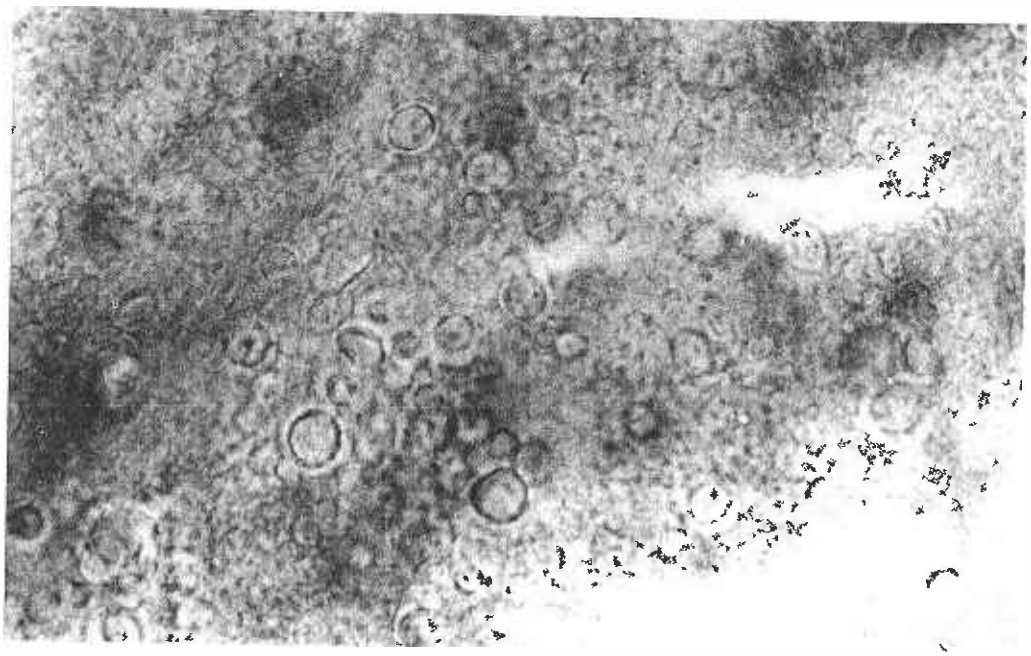

Fig 1D. This picture illustrates the importance of a high index of suspicion for the diagnosis of cryptococcosis. The highly refractile nodules are the spores of the fungi and can easily be mistaken for particles of starch (Papanicolaou x 1000).

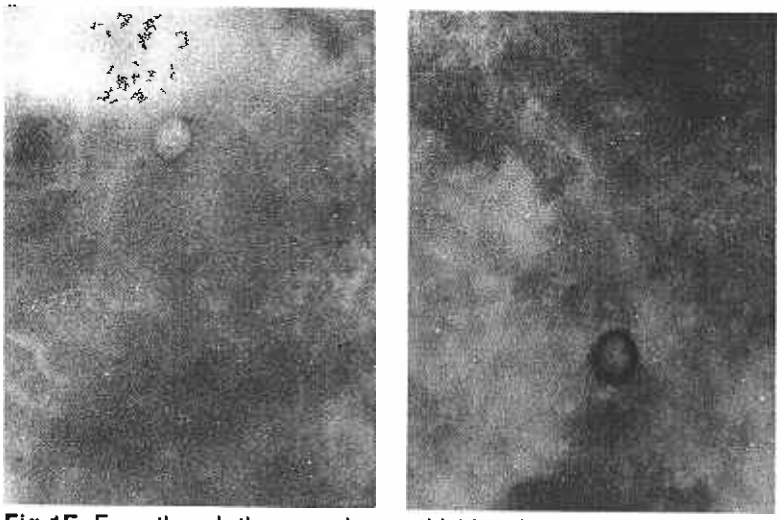

Fig 1E. Even though the capsules are highly refractile, they can still be overlooked if special stains for the fungi are not used. Routine Papanicolaou stain was used on the left whilst that on the right was stained with mucicarmine. Note how brilliantly the capsule stains (x 1000).

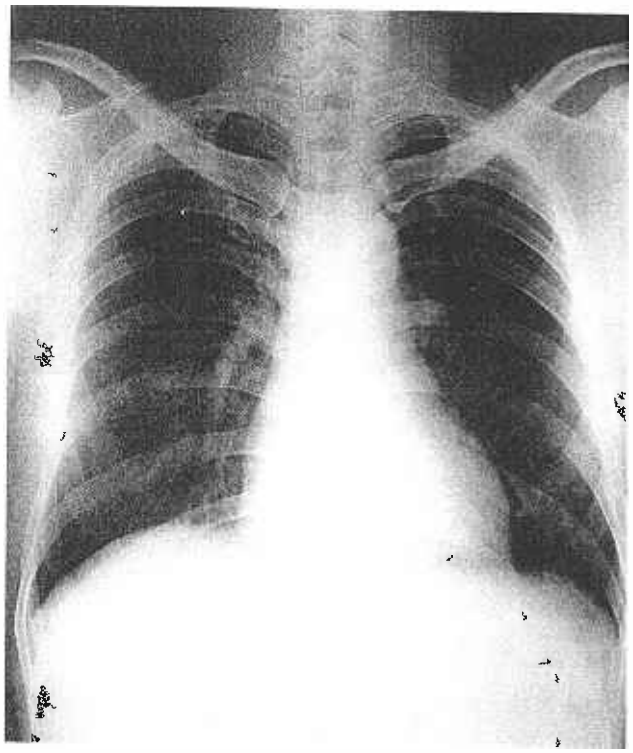

Fig 1F. Four months after intra-venous Amphotericin B. Only residual fibrosis is seen.

radiographic appearance suggested the possibility of an arterio-venous malformation (Fig. 1C). Clinically, no bruit was heard over the precordium. Full lung function tests did not reveal the presence of a shunt. The pulmonary angiogram was normal. The lesions in the superior segment of the right lower lobe felt firm on percutaneous lung aspiration. The aspirate yielded Crypyococcus neoformans (C. neoformans) on culture and special stains with mucicarmine identified the organism on the smear (Figs. 1D & E). Because the lesions were multiple and were not only increasing in size but in number, specific antifungal therapy was instituted with marked improvement noted at the end of the treatment (Fig. 1F). A search for central nervous system (CNS) and renal involvement was negative.

The second patient, a seventy year old male asthmatic nonsmoker, presented to us in 1986 with a persistent cough for the last two months. The cough was productive of a small amount of whitish sputum but there was no haemoptysis. There was no history of recent weight loss ans he was afebrile. Except for a few episodes of breathlessness, which were treated by a general practitioner, there was no history of note. On physical examinatio, there were a few lung crepitaions and rhonchi. No other abnormality was found. He was not on long term steroid therapy nor was he diabetic. The chest radiograph revealed a fairly well defined lesion in the right lower zone and a vague lesion slightly more superiorly (Figs. 2A & B).

Illustrations — Patient 2

Figs 2A & B. Two lesions are seen in the right middle lobe. A coin lesion is seen inferiorly and an infiltrate superiorly.

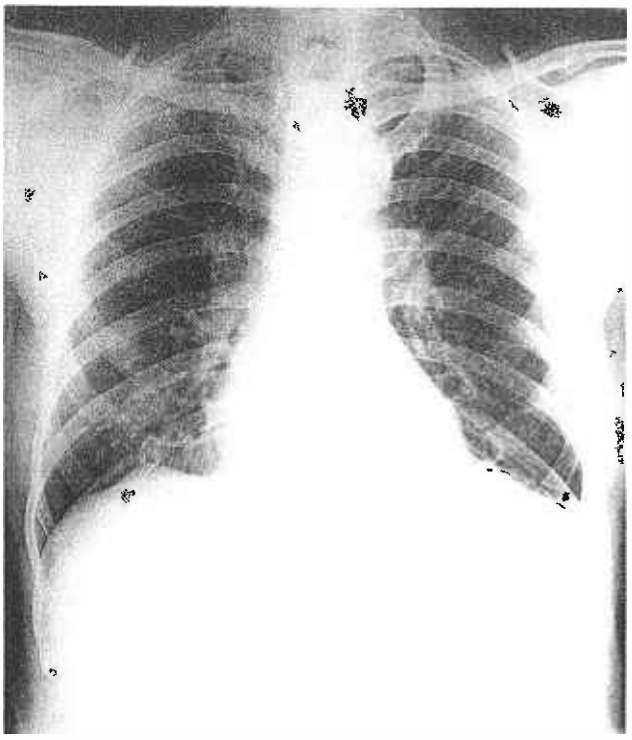

Fig. 2A

Tomography delineated the lesions better and showed a well defined lesion in the right middle zone measuring about 3x2 cm with a small cavity superiorly. The second lesion was an ill defined infiltrate. A percutaneous aspiration revealed C. neoformans (Figs. 2C & D). The cerebrospinal fluid (CSF) was normal. Intravenous Amphotericin B was given. Within a month, the lesions became more well defined and the last radiograph done about four months later showed only minimal residual fibrosis. The patient has remained well since.

The next patient, a sixty-four year old male was first seen at SATA (Singapore Anti-Tuberculous Association) in January 1986 with a history of 7-8 months of cough productive of small amounts of mucoid sputum. There were two episodes of blood stained sputum together with some loss of weight and loss of appetite. The patient used to smoke 30-40 cigarettes a day for many years but had stopped for the last three years. There was no history of diabetes but he had pulmonary tuberculosis many years ago. The physical examination was essentially normal. The chest radiograph revealed an ill defined opacity in the right upper lobe (Figs. 3A & B). In view of his age and history of smoking, the diagnosis was a carcinoma. However, bronchoscopy revealed a normal tracheo- bronchial tree and brushings showed C. neoformans. The patient was advised admission but refused although he now complained of an intermittent headache. The physical examination was normal. However, two weeks later, the patient returned to the hospital complaining of severe and persistent headaches and was admitted. Again, the physical examination was negative but the CSF and sputum smears were positive for actively budding cryptococci. A lobectomy was performed on 20 June 86 after intravenous Amphotericin B was started. The patient responded and there was conversion of both the sputum and the CSF.

The fourth patient was a sixty-six year old diabetic female who had a carcinoma of the uterus four years ago in 1981. A total hysterectomy and bilateral oophorectomy was done and a course of radiotherapy was given. Two years later, she had a gastrectomy for a carcinoma in the stomach. It was uncertain if this was a primary lesion or a secondary from the carcinoma of the uterus. The present illness started only a month ago in August 1985. The patient presented with an unproductive cough and a left sided chest pain. A chest radiograph showed a lesion in the left lower lobe and the diagnosis was that of a metastatic deposit (Figs. 4A & B). A percutaneous aspirate showed malignant cells indicative of poorly differentiated adenocarcinoma as well as fungal forms of cryptococci engulfed within giant cells. Computerised tomography

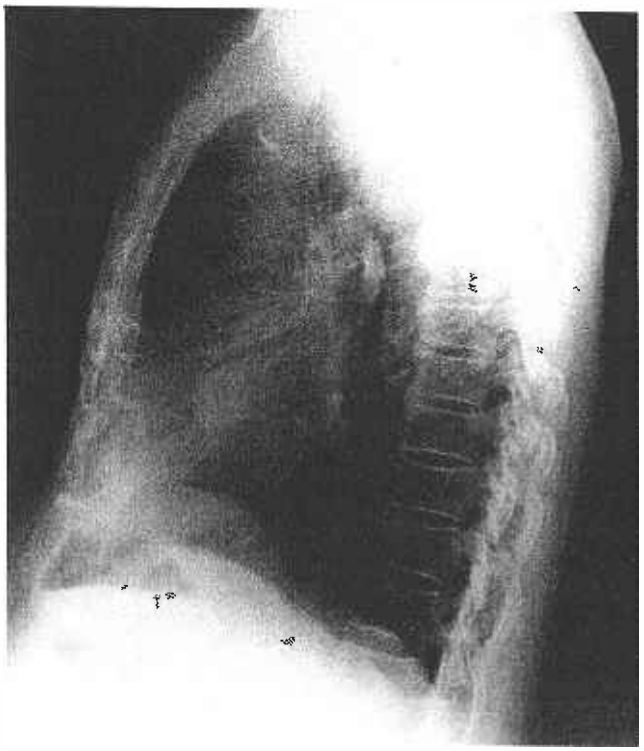

Fig. 2B

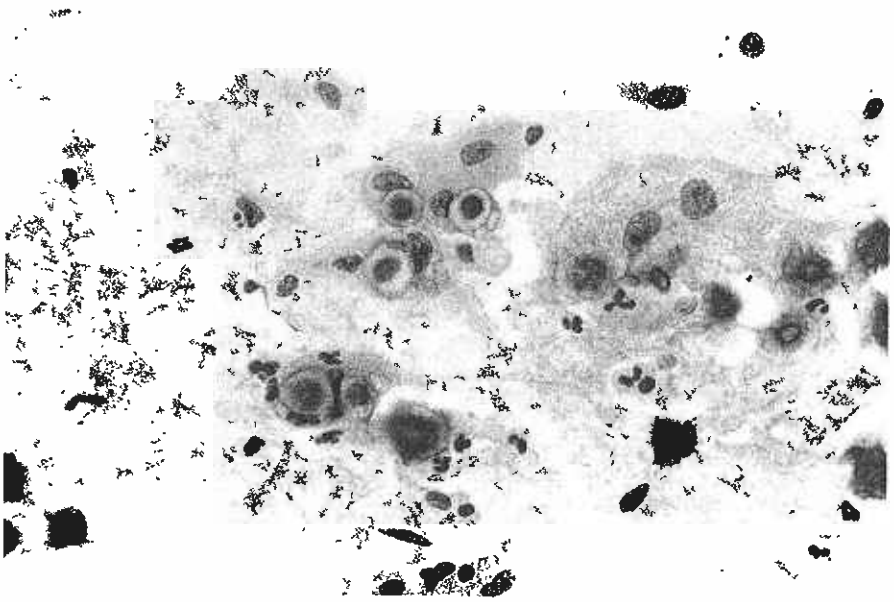

Fig 2C. Multiple cryptococci stained with mucarmine. Note the thick capsules (x 132).

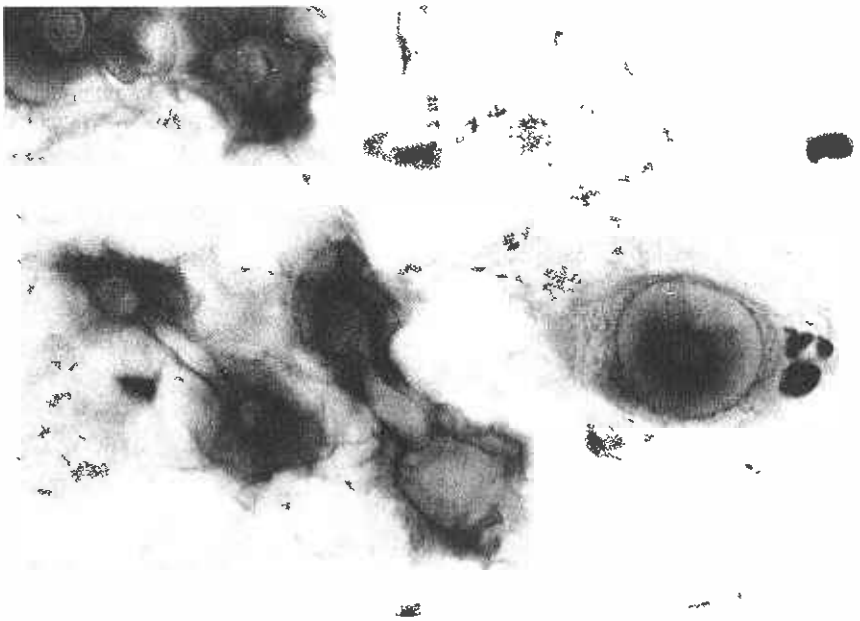

Fig 2D. With mucicarmine, the capsules also contract and this gives it a characteristic appearance which is typical for the organism (x 1000).

Illustrations — Patients 3, 4 & 5

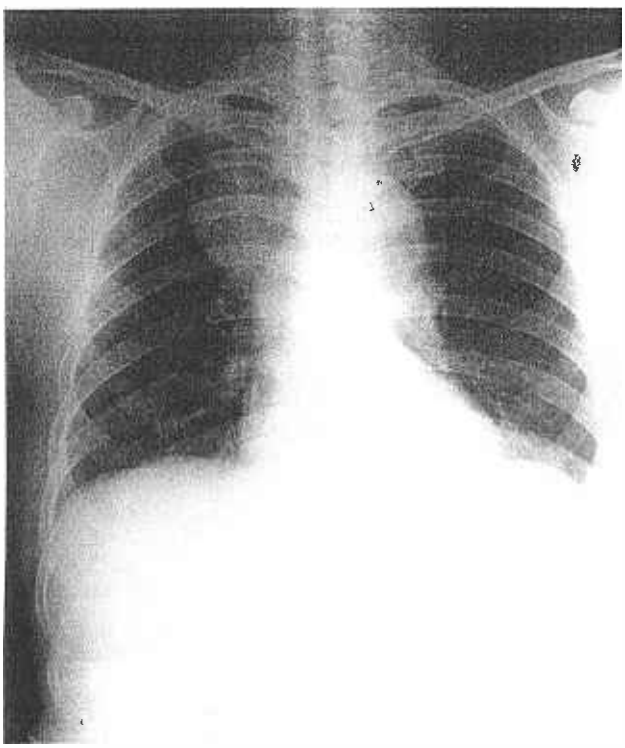

Fig. 3A

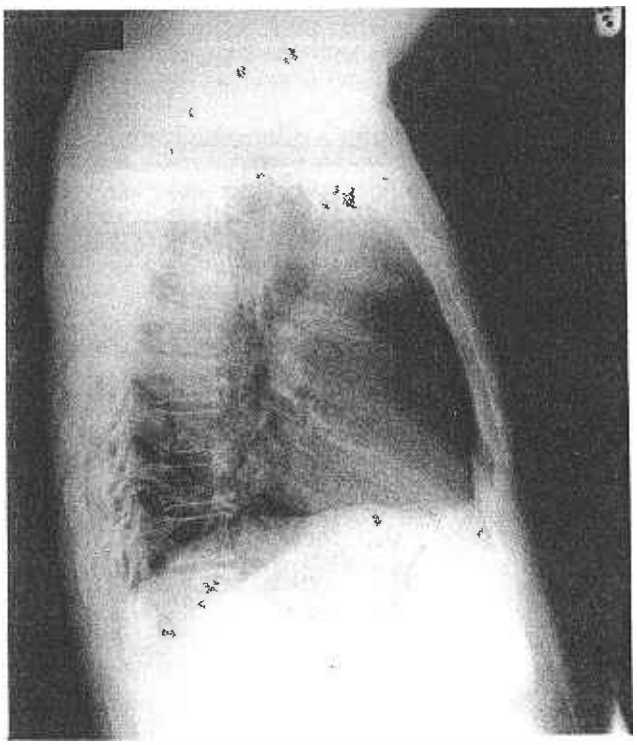

Fig. 3B

Figs 3A & B. An opacity is seen in the anterior segment of the right upper lobe.

showed a single nodule confined to the left lower lobe and an isotope bone scan showed no metastases. As the lesion was localised, a lobectomy was advised. At operation, a 8x6x6 cm lesion attached to the lateral chest wall was seen. This was confirmed to be a focus of metastatic adenocarcinoma. In addition, there was another nodule proximally, close to the hilum, which histologically showed multiple granulomas containing cryptococci with surrounding fibrosis and chronic inflammation. The patient made an uneventful recovery.

Figs 4A & B. A nodule is seen in the basal segment of the left lower lobe.

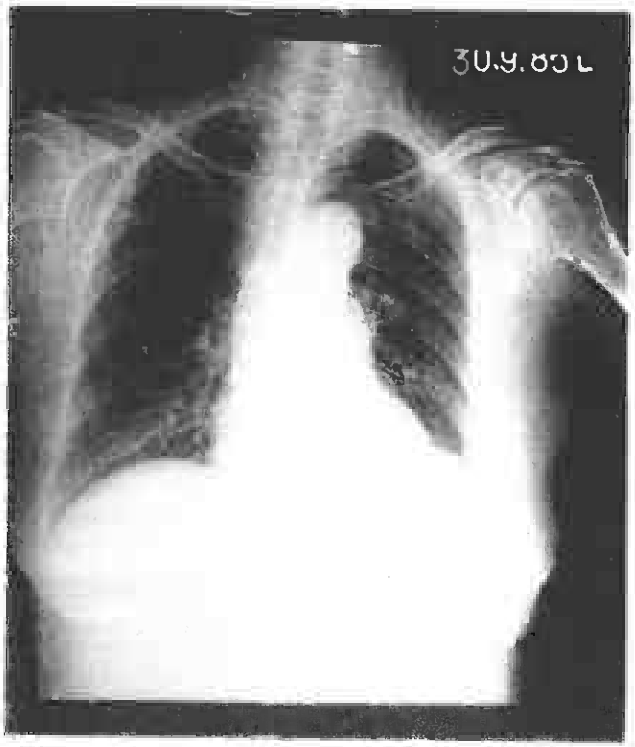

Fig. 4A

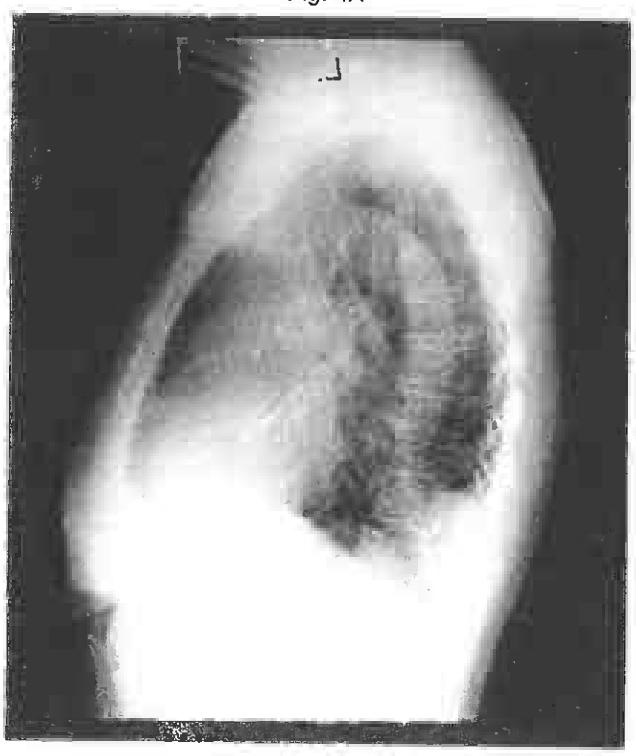

Fig. 4B

Figs 5A & B. Bronchogram study. A large and well defined opacity is seen in the right middle and lower zones. The bronchi around the mass are displaced and compressed. No other pulmonary lesions were noted.

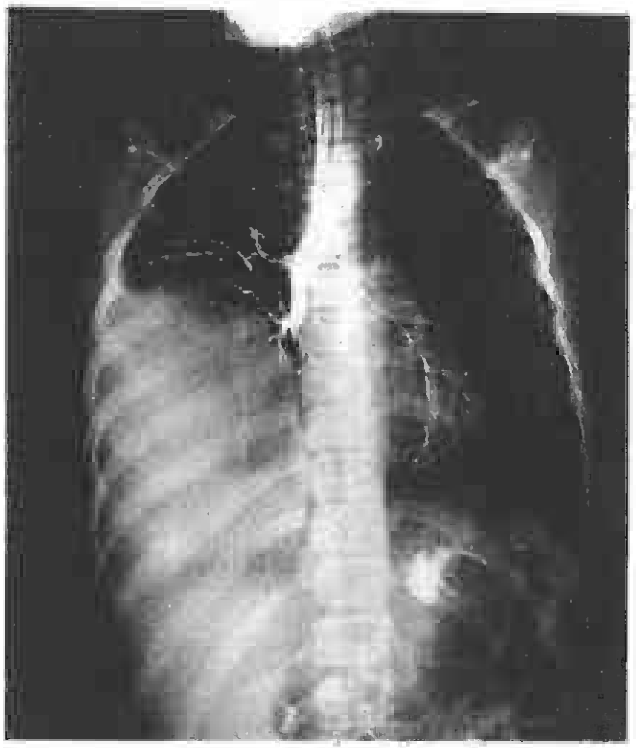

Fig. 5A

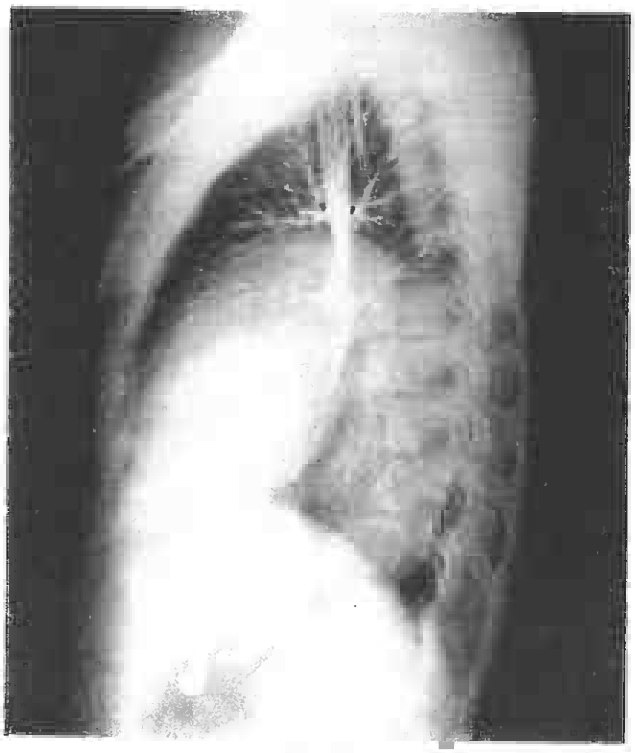

Fig. 5B

The last patient was a ten year old girl seen in October 1976 with acute respiratory distress. She had a cough for two months and was brought in slightly breathless. She was also having a swinging fever. Crepitations were heard in the right lung base with evidence of consolidation. The investigations were inconclusive except that the lesion seen on the chest radiographs was intrathoracic in origin (Figs. 5A & B). In view of the large mass, a tumour rather than an infective cause was suspected. An exploratory thoracotomy was performed. Unfortunately, the lesion was too large with involvement of both middle and lower lobes

as well as the neighbouring structures and a partial resection was done. The histology revealed massive cryptococcosis. Two days later, she developed meningeal signs and the CSF was positive for the organism. She was treated with Amphotericin B and made good progress. Unfortunately, she developed liver failure as a consequence of the therapy and died a few months later.

DISCUSSION

Cryptococcus neoformans, also known as Torula histolytica, is a nonmycelial budding yeast. The name Torula histolytica was coined by Stoddard and Cutler in 1916(1) because they believed the mucoid component of the lesions was due to the histolytic effect of the organism on the tissues. When this effect was shown to be due to the abundant capsular material, many observers adopted the name C. neoformans. Both are used interchangeably. C. neoformans is a cosmopolitan disease of man and Zenker in 1861, described an organism of yeast-like nature from a pharyngeal infection of a man. In 1894, a cryptococcal infection was reported in a gumma like lesion from the tibia of a woman by Busse(2) and the first case of pulmonary cryptococcisis was only reported in 1924 by Sheppe(3). The disease begins primarily as a respiratory infection which may then spread to the CNS or other organs, namely the kidneys and the skeletal system; but the organism has been cultured from almost any organ in the disseminated form. The CNS is the commonest site of involvement clinically and is fatal if untreated. The next most common site is the lungs. However, in a post mortem series, the organism was found in almost equal frequency in the CNS as well as the pulmonary system(4). The primary infection of the lung may or may not be symptomatic. Isolated pulmonary disease was said to be rare because of the difficulty in identifying the organism as well as the lack of awareness of the protean manifestations of the disease. Recent figures put the incidence of isolated pulmonary involvement at between 15-30% of cases of cryptococcosis (5,7). One third of the pulmonary cases are asymptomatic (6,7) and only 10% of these have a serious coexisting disease(7). The disease is encountered more frequently in the immunocompromised host and is especially seen in malignancy of the recticuloendothelial system - Hodgkin's disease, lymphomas and leukemia. Diabetes and patients on long term steroids are also susceptible. Normal serum is said to inhibit the growth of the organism and with a change in the immune status, the organism is allowed to manifest itself(6). The source is mainly from the excreta of birds especially pigeons which carry the organism physically in their feet and beaks. They themselves are only moderately susceptible experimentally. Spontaneous infection has not yet been demonstrated in birds.

The disease has been described mainly in whites. Although all ages are susceptible, two thirds are between the third to the sixth decades. Men are affected more frequently than women(6,7). Of the 101 cases reviewed by Campbell, 87% were whites and 82% were males. Spontaneous cases of cryptococcosis have been reported although bird handlers and residents of New York City (where pigeons are in abundance) have a higher incidence. In none of our patients was there a history of exposure to any birds. The average age of the five patients was 48.6 years. There were three males and two females. There was no history of immunosuppression except possibly in one (patient 4) who had malignancy as well as diabetes. Two had meningeal spread while two had disease confined to the lungs. The central nervous system status of the 4th patient was not known.

Primary pulmonary infection as mentioned before, is asymptomatic in a third of the diagnosed cases. In our five cases, two were asymptomatic. The pulmonary disease follows a subacute or chronic course with minimal constitutional signs and symptoms. When pulmonary involvement becomes clinically apparent, the signs and symptoms in order of frequency are cough, chest pain, mucoid sputum production, weight loss, low grade fever, infrequent haemoptysis, pleuritic pain, dyspnoea, infrequent night sweats and malaise. The appearance of the chest radiographs varies considerably but usually takes one or a combination of three forms. The most commonly encountered one is the pseudotumour which is either solitary or multiple with hardly any surrounding reaction. Cavitation was said to be rare initially but Campbell in a review of the English literature in 1966 found an incidence of 16%(7). The second radiological appearance is that of a disseminated nodularity which is not unlike that of miliary tuberculosis. There may or may not be accompanying linear infiltrates. In fact, cryptoccocsis may mimic tuberculosis completely not only in the lungs but also in the CNS as well as in the skeletal system. The third form is that of an infiltrative process of varied appearances; either interstitial or alveolar. Regional lymphadenopathy is conspicious by its absence(8) but a more recent article by Feigin in 1983(9) quoted a higher incidence and Wolfe(10) in his 21 cases noted lymphadenopathy in a small percentage of his patients. He also noted that lymphadenopathy was a late mainfestation. Although predilection for the lower lobes were cited by Kuydendall et al in 1957(11), Littman and Zimmerman in 1956(8), Bonmati et al in 1956(12) and Campbell in 1966(7), Wolfe and Jacobson in 1958(10) and Gordonson et al in 1972(5) found a predilection in the upper lobes while other authors, Hatcher in 1971(13), Hammerman et al in 1973(14) and Feigin in 1983(9) found no predilection of involvement. Although we have only five cases, they appear to support the observation that there is no predilection for any lobe. We had one case each with right middle lobe, right upper lobe and left lower lobe involvement (Patients 2, 3 & 4 respectively), another with multiple nodules in the right upper lobe, right lower lobe and left upper lobe (Patient 1) and one with massive disease of the right middle lobe and right lower lobe (Patient 5). Pleural effusion is rare with fewer than twenty cases reported up to 1972(15). As the cultures are frequently negative (50%), early diagnosis is often difficult. The eosinophil count however has been noted to be high and this should alert the clinician to the possibility of a cryptococcal effusion. In a postmortem study of thirty-seven patients with pulmonary cryptococcosis, Salyer(16) found seven cases with pleural involvement. All were unilateral and were bloody on aspiration. Five were on the right side. All were associated with a subpleural nodule and the effusion was thought to be the result of spread from this nodule. In the past, the finding of C. neoformans in the sputum was considered to be evidence of pulmonary involvement with the disease. Recently, Reiss and Szilagyi(17) recovered the organism from six out of the ninety-two patients with malignant disease, none of whom were symptomatic, thus indicating a carrier state in man.

The tissue reaction is related to the duration of the disease. Early lesions are gelatinous while older lesions are granulomatous. On routine Papanicolaou staining in aspirates, the organism may be missed or mistaken for artefacts. Histochemical stains including Gomori methanamine silver and Periodic acid- Schiff aid in identification, while positive capsular staining with Mayer's mucicarmine stain is considered diagnostic(18). With healing, the lesions frequently leave no trace of the disease. Some may heal by fibrosis and some may even calcify but these are considered rare(8).

A point to stress in the diagnosis of pulmonary cryptococcosis is the tissue diagnosis. Of the 101 cases reviewed by Campbell(4), only 19 were diagnosed by cultural methods. Sixty two were diagnosed by surgical intervention which included percutaneous aspirations. Nine

were diagnosed by autopsy and in the remaining 11, the method of diagnosis was not specified. In our five cases, all were diagnosed by interventional means; three by percutaneous aspirations, one by bronchoscopy and the remaining one by thoracotomy.

Once the diagnosis has been established, the next question that arises is that of treatment. Should the lesion be treated; and if so by surgery or by chemotherapy or a combination of both? Based on the report from the Centre for Disease Control Cooperative Mycoses Study(14), a report based on their experience with 80 cases as well as a review of the Literature, of the 36 patients with primary pulmonary cryptococcosis treated with Amphotericin B alone, 33 did well. Only one patient failed to respond and still had C. neoformans in his sputum after treatment and two others died of progressive pulmonary involvement. Of the 92 cases treated by surgery alone, only 3 developed meningitis after surgery. None of the 15 patients treated with Amphotericin B in addition to surgery developed late sequelue. Twenty eight patients who had only pulmonary involvement and who were not terminally ill received no specific antifungal treatment. Of these 28 patients, 5 (17.9%) developed significant morbidity. Two developed central nervous system involvement, 1 died of progressive pulmonary disease and two eventually required Amphotericin B treatment. The available clinical data as well as the radiographic appearances were reviewed in an attempt to correlate the risk of developing meningitis. There was no significant difference in the incidence of meningitis between those operated on for a solitary lesion and those operated on for an infiltrate or a mass lesion. There was also no significant difference in the incidence of meningitis in those who had symptoms and those who had none. The authors concluded that most patients will recover without treatment and for those who received treatment, Amphotericin B alone or surgical resection alone resulted in similar rates of morbidity. In view of the toxicity associated with Amphotericin B treatment, a 3% rate of meningitis occuring after surgery would not seem to justify routine use of the drug as a prophylaxis for prevention of meningitis in surgically treated patients. The authors also included a guideline to the management of patients whose sputum or lungs contain cryptococci: (1) Before making a diagnosis of pulmonary cryptococcosis, extrapulmonary lesions should be carefully searched for.(2) Since most patients with primary pulmonary cryptococcosis do well without treatment, a period of close observation for approximately 1-2 months is justified.(3) For those patients who are to have treatment, a full course of intravenous Amphotericin B or surgical resection offers similar results; one is not superior to the other.(4) For patients with positive sputum cultures, normal CSF, and no evidence of disease (i.e. colonization), there is little risk of developing meningitis or pulmonary invasion; therefore no specific treatment is needed, although close follow up is necessary as meningitis due to cryptococcosis carries with it a mortality of 30-35%.

SUMMARY

Pulmonary cryptoccocosis is protean in its radiologic manifestations. Infection is through inhalation and dissemination is via the blood stream. The lungs alone can be affected and if so the disease is benign and self limited. In 1/3 of the patients, the disease is asymptomatic. Only in 10% is there a serious coexisting disease. In the lungs, the radiographic appearance may take one or any combination of three forms. The commonest is the pseudotumour which may be single or multiple. One or more lobes may be involved. The second pattern of involvement is that of miliary shadowing which may be mistaken for tuberculosis. The third is an infiltrative process. The course of the disease is usually subacute or chronic and cryptococcosis should be included in the differential diagnosis when considering a pulmonary disease of slow evolution, such as primary or secondary carcinoma, tuberculosis, pneumoconiosis, sarcoidosis as well as other fungal infections. When only the airways are colonized, the chest radiograph is normal and the diagnosis is made by sputum culture or cytology. The organism may be difficult to culture and in many cases tissue diagnosis is necessary. As skin tests and serologic tests are of limited value, percutaneous lung biopsy is playing an ever increasing role in the diagnosis of cryptococcosis. The awareness of the disease is of course the key to the diagnosis. Not all cases need treatment. As mentioned before, most are benign and are limited to the lungs. If treatment is necessary, both intravenous Amphotericin B and surgery give similar results and there is no necessity to give prophylaxic Amphotericin B prior to surgery.

ACKNOWLEDGEMENT

The authors are grateful to the Medical Departments of I, II and III of Tan Tock Seng Hospital for patients 3, 4 & 5 and 1 & 2 respectively.

REFERENCES

1. Stoddard JL and Cutler EC. Torula infection in man. Rockefeller Institute for Medical Research, Monograph 6, Jan. 31, 1916.

2. Busse, O. Ueber Saccharomycosis hominis. Virchows Arch path Anat. 1985; 140:23-32.

3. Sheppe WM. Torula infection in man. Amer J Med Sci. 1924; 167:91-108.

4. Lewis J and Rabinowich S. The wide spectrum of Cryptococcal Infection. JAMA 1972; 53:315-322.

5. Gordonson J, Birbaum W, Jacobson G and Sargent EN. Pulmonary Cryptococcosis. Radiology 1974; 112:557-561.

6. Littman ML and Walter JE. Cryptococcosis: Current Status. JAMA 1978; 45:922-927.

7. Campbell GD. Pulmonary Cryptococcosis. Am Rev Resp Dis. 1966; 94:236-243.

8. Littman ML and Zimmerman LE. Cryptococcosis. New York, Grune and Stratton, 1956.

9. Feigin DS. Pulmonary Cryptococcosis: Radiologic-Pathologic Correlates of its three forms. AJR 1983; 141:1263-1272.

10. Wolfe JN and Jacobson G. Roentgen manifestations of Torulosis (Cryptococcosis). Am J Roentgenol 1958; 79:216-227.

11. Kuykendall SJ, Ellis FH, Weed LA and Donoghue FE. Pulmonary Cryptococcosis. New England Journal of Medicine 1957; 257:1009- 1016.

12. Bonmati J, Rogers JV and Hopkins WA. Pulmonary Cryptococcosis. Radiology 66; 1956:188-194.

13. Hatcher CR, Sehdeva J, Waters WC, Schulze V, Logan WD, Symbas P and Abbott OA. Primary pulmonary cryptococcosis. Journal of Thoracic and Cardiovascular Surgery 1971; 61:39-49.

14. Hammerman KJ, Powell KE, Christainson CS, Huggin PM, Larsh HW, Vivas JR and Tosh FE. Pulmonary Cryptococcosis: Clinical forms and Treatment. Am Rev of Resp Dis 1973; 108:1116-1123.

15. Ebstein R and Hurt KK. Pleural effusion secondary to Pulmonary Cryptococcosis. Chest 1972; 61:296-298.

16. Salyer WR and Salyer DC. Pleural involvement in Cryptococcosis. Chest 1974; 66:139-140.

17 Reiss F and Szilagyi G. Ecology of yeast-like fungi in a hospital population. Detailed Investigation of Cryptococcosis neoformans. Arch Dermat 1965; 91:611-614.

18. Baker RD and Haugen RK. Tissue changes and tissue diagnosis in cryptococcosis. Am J Clin Path 1955; 25:14-24.