

# CRYPTOCOCCOSIS IN PAKISTAN

Pages with reference to book, From 51 To 53

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## INTRODUCTION

Cryptococcal meningitis is a relatively uncommon but treatable fungal infection of the central nervous system (CNS). *Cryptococcus neoformans*, the etiologic agent of cryptococcosis, is an encapsulated yeast that produces CNS disease with clinical and laboratory features easily confused with tuberculous meningitis. Untreated, cryptococcal meningitis is invariably fatal, thus making differentiation from tuberculosis crucial. We present three recent cases of cryptococcal meningitis in Pakistan, and discuss the clinical and epidemiological significance of these findings. Clinicians are urged to exclude cryptococcus as a cause of chronic lymphocytic meningitis in Pakistan.

## CASE 1

A 57 year-old man was admitted to AKUH in November 1986 with the complaints of low-grade fever and headache since 2 months and recent confusion followed by somnolence. One year prior to admission he had received carbamazepine for treatment of tic douloureux. Neutropenia, present for nine months, had been attributed to carbamazepine therapy. He had also been treated for *Legionella pneumophila* pneumonia in August 1986, with complete recovery. Neurological examination revealed lethargy but no focal deficits. Multiple lumbar punctures and routine studies showed CSF abnormalities (WBC = 121/mm<sup>3</sup> with 89% lymphocytes; protein 114 mg/dL; glucose 21 mg/dL) but failed to yield a diagnosis. There was no response to empiric antituberculous treatment. An India ink smear of CSF was requested and revealed the presence of numerous budding yeast forms; *Cryptococcus neoformans* was subsequently recovered in culture from this specimen. A cryptococcal CSF antigen demonstrated a titer of 1:640. The patient was begun on amphotericin B intravenously, and a ventriculoperitoneal (VP) shunt was required because of obstructive hydrocephalus. Bone marrow biopsy demonstrated a well-differentiated non-Hodgkin's lymphoma, but the malignancy was thought to be of an indolent nature and cytotoxic chemotherapy was withheld so as not to worsen the immunosuppression. The patient received a total of 2.1 grams of amphotericin B, and there was marked clinical improvement in his level of consciousness and mentation and his CSF cryptococcal antigen fell to 1:2. His later course was complicated by CSF shunt malfunction and by subdural hematoma formation following VP shunt replacement. The patient ultimately died from nosocomial *Pseudomonas* and *Candida* spesis.

## CASE 2

A 52 year-old woman was hospitalized at AKUH because of fever of 3-4 weeks duration and excessive drowsiness for three days prior to admission. Posthepatic cirrhosis had been diagnosed 2 years previously. On admission she was febrile to 38.5°C with hepatomegaly and ascites. She was lethargic but rousable with no signs of meningeal irritation or motor/sensory focality. Serum ammonia level was within normal limits. *Klebsiella pneumoniae* was recovered from ascitic fluid and a diagnosis of spontaneous bacterial peritonitis was made. Appropriate antibiotics resulted in clinical improvement but the patient remained febrile. On the tenth hospital day she became incoherent and disoriented. Examination of CSF revealed 221 WBCs/mm<sup>3</sup> (predominantly lymphocytes), protein 101 mg/dL, and glucose 34 mg/dL. A smear for acid fast bacilli was negative, and a chest radiograph revealed no evidence of active or chronic disease. Yeast forms were seen on an India ink smear of CSF, and the

culture grew *C. neoformans*. The patient was begun on systemic amphotericin B, but he died three days later as a result of a massive upper gastrointestinal hemorrhage.

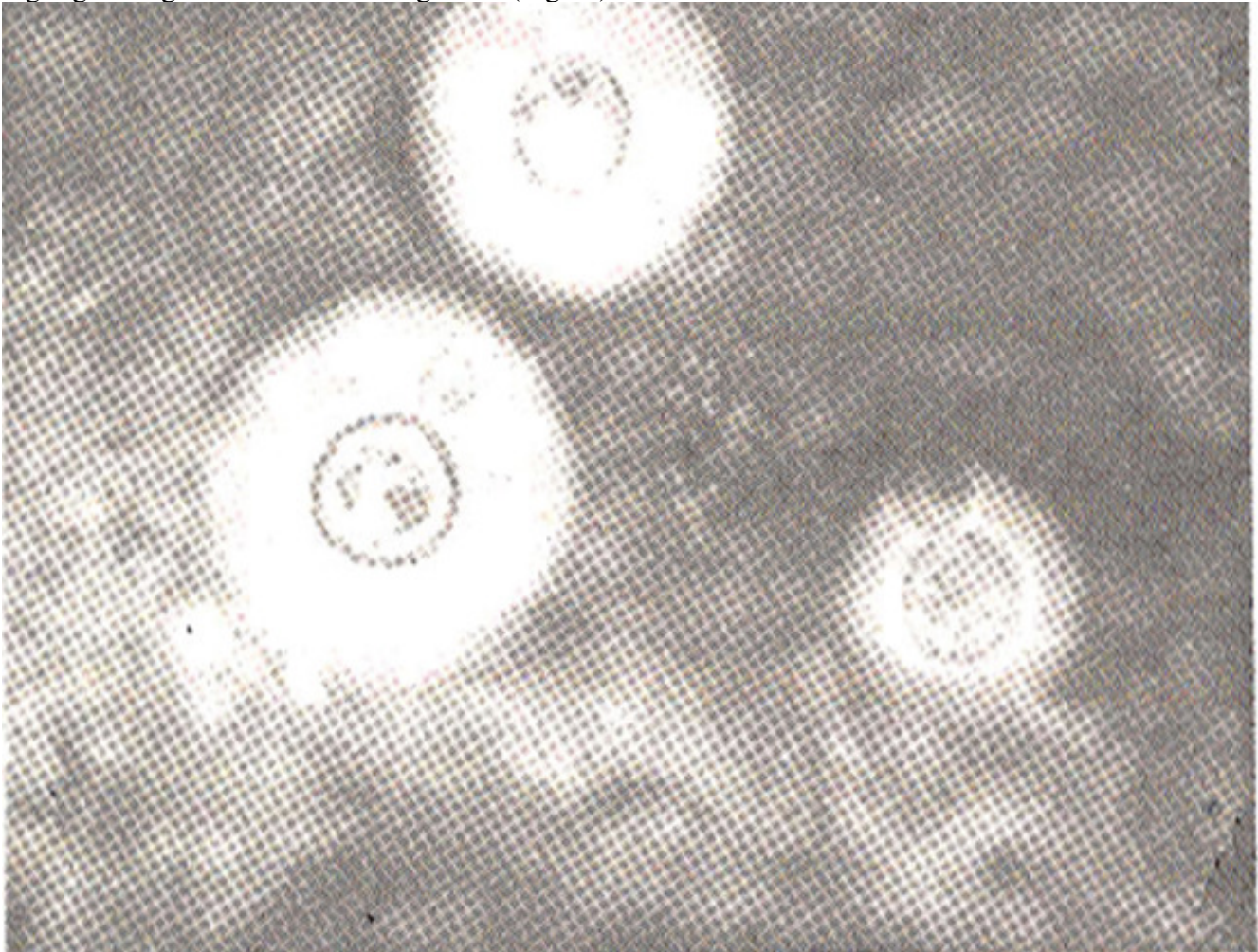
### **CASE 3**

A 46 year-old man was admitted to the hospital with fever and headaches of 2 weeks duration, and recent aphasia. Hodgkin's lymphoma had been diagnosed in 1980, and he had received multiple courses of chemotherapy. In October 1986 he was hospitalized with a pathologic fracture of the left 8th rib, and biopsy of the rib revealed yeast forms on histologic section. No symptoms or signs of CNS infection were present at that time and he was not given any antifungal therapy. At the time of last admission, examination of the CSF showed numerous yeast cells of *Cryptococcus neoformans*. Systemic amphotericin B therapy was initiated, but the patient died of presumed septicemia on the second day of treatment.

### **DISCUSSION**

*Cryptococcus neoformans* is a yeast-like fungus and a saprobe in nature, with a worldwide distribution in both, temperate and tropical regions. The organism is found in pigeon droppings as well as in soil and other environmental samples, and may reach high concentrations in urban areas<sup>1</sup>. While most human cases of cryptococcosis have been reported from the United States, the disease has been well recorded in India, Malaysia, the Far East, Africa, Australia, and South America.<sup>2</sup> Skin test surveys have suggested subclinical infection in significant numbers of apparently normal individuals. The epidemiology of *Cryptococcus neoformans* has not been closely studied in Pakistan. The primary site of infection is the lungs, acquired via respiratory inhalation of the fungus and generally causing subclinical infection. Man-to-man transmission does not occur.<sup>3</sup> The most common clinical form of the disease is meningitis, which develops by way of hematogenous dissemination from the lung to the central nervous system (CNS). Less commonly, symptomatic pulmonary or cutaneous infection or blood-borne disseminated disease may be seen. The onset of cryptococcal meningitis is usually slow and closely resembles other forms of chronic meningitis such as tuberculosis.<sup>4</sup> Dull occipital headache, fever, drowsiness, and alterations of consciousness or behaviour may be presenting features. Visual impairment may also develop. On examination, stiffness of the neck is often found and focal neurologic deficits may be elicited. Progression is slow in most cases, but the process is ultimately fatal if the patient is not treated. As with clinical features, the laboratory parameters of cryptococcal meningitis typically mimic tuberculous meningitis. There is a mononuclear pleocytosis with elevated cerebrospinal fluid (CSF) protein concentrations and normal-to-low glucose levels. If available, a CAT scan of the head may be helpful in excluding associated hydrocephalus, or rare solid cryptococcoma. Other sites of dissemination include skin, bone, prostate, and retina. Cutaneous cryptococcosis occurs in about 10%-15% of patients. Types of cutaneous lesions include ulcers, granulomas, nodules, and cellulites. Osseous cryptococcosis is often slightly painful, and lytic lesions are seen on radiography. Even in the absence of clinical signs approximately half of these persons with skin or bone involvement have or will develop meningitis, making lumbar puncture and CSF examination mandatory. Visceral invasion of the liver, spleen, and kidney occurs mainly in widely disseminated cases. Cryptococcosis is most often an opportunistic infection occurring in immunocompromised individuals with impaired T-cell-mediated defence mechanisms.<sup>5</sup> Such hosts include persons receiving corticosteroids and cytotoxic agents, tissue transplant recipients, patients with the acquired immunodeficiency syndrome (AIDS), alcoholics, persons with leukemia or lymphoma, or those with chronic hepatic or renal disease. However, as many as 25%—50% of cases may occur in apparently normal, immunocompetent individuals.<sup>6</sup> In a country like Pakistan where tuberculosis is endemic, and cases of chronic lymphocytic meningitis are typically presumed to be tuberculous in origin, it is imperative to exclude

other treatable causes of CNS infection such as cryptococcosis. The diagnosis of cryptococcosis can be confirmed by visual demonstration or cultural isolation of the organism. In addition, if available, the latex test for demonstration of cryptococcal antigen in CSF and serum is very helpful.<sup>7</sup> While the organism grows readily on Sabouraud's agar, where culture means are not present, the India ink preparation is the simplest and most rapid diagnostic approach. One or two drops of centrifuged CSF are mixed on a glass slide with the same amount of India ink, a cover-slip set in place, and the specimen is examined under the light microscope. The polysaccharide capsule of the yeast is highlighted against the black background (Figure).



**Figure. Budding yeast forms of cryptococcus neoformans on India Ink Smear.**

The combination of amphotericin B and 5—fluorocytosine is the antifungal regimen of choice for cryptococcal meningitis but where the latter agent is not available parenteral amphotericin B alone, if given for 8—10 weeks, produces acceptable cure rates.<sup>8</sup> Local instillation of amphotericin B into the CSF via intraventricular or intralumbar injection is only occasionally required, and is associated with side effects such as chemical arachnoiditis.

## REFERENCES

1. Diamond, R.D. *Cryptococcus neoformans*, in Hunter's tropical medicine, edited by G.T. Strickland

Sydney, Saunders, 1984, p. 463.

2. Hey, R.J. Cryptococcosis, in Principles and practice of infectious diseases, edited by G.L. Mandel et al. Brisbane, Wiley, 1979, p. 23.

3. Littman, M.L. and Walter, J.E. Cryptococcosis; current status. *Am. J. Med.*, 1968; 45: 922.

4. Ellner, J.J. and Bennett, I.E. Chronic meningitis. *Medicine*, 1976;55: 341.

5. Schimpff, S.C. and Bennett, I.E. Abnormalities in cell-mediated immunity in patients with *Cryptococcus neoformans* infection. *J. Allergy Clin. Immunol.*, 1978;43:430.

6. Diamond, R.D. and Bennett, J.E. Prognostic features in cryptococcal meningitis: A study of 111 cases. *Ann. intern. Med.*, 1974; 80:176.

7. Bindschadler, D.D. and Bennett, J.E. Serology of human cryptococcosis. *Ann. Intern. Med.*, 1968;69:45.

8. Bennett, J.E., Dismukes, W.E., Duma, R.E., et. al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N. Engl. J. Med.*, 1979; 301 : 126.