

CRYPTOCOCCAL MENINGITIS IN SINGAPORE

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SYNOPSIS

Twenty-one cases of cryptococcal meningitis have occurred during the past two years, twelve in 1974 and 9 cases in 1975. From the figures available from our local literature 30 proven cases have been reported during a period of 11 years from 1959-1970 showing that there has been an increase in incidence during the past two years. All cases reported during the past two years were confirmed by isolation of the organism from cerebrospinal fluid. Cryptococcal meningitis constitutes 23.7% of fungal and pyogenic meningitis reported by the bacteriology laboratory during the past two years.

INTRODUCTION

Cryptococcosis is an infectious disease of man and animals resulting from inhalation of a yeast like fungus called *Cryptococcus neoformans*. The organism is abundantly found in pigeon excreta and soil. The primary infection is in the lungs following inhalation of the organism. It may be localised to the lungs or disseminated to any part of the body especially to the brain and meninges and the spinal cord. Painless skin lesions such as papules, pustules and ulcers occur in 10% of the cases. The disease affects all ages, two-thirds of the cases are between the age group of 30-50 years. It is uncommon before puberty. Predisposing factors which result in infection are Hodgkins disease, lymphosarcoma, leukaemia and diabetes mellitus.

In cerebral cryptococcosis there are signs and symptoms of meningitis, meningo-encephalitis or a space occupying lesion. A cryptococcal granuloma localised in the brain or spinal cord may show signs suggestive of a tumour, abscess or subdural haematoma. In most cases the clinical picture closely resembles tuberculous meningitis. In the early stages the C.S.F. does not show any changes except the presence of the organism *C. neoformans*; hence the importance of gram staining a centrifuged deposit of the C.S.F. and examining this under the microscope. As the disease progresses the changes in the C.S.F. are indistinguishable from tuberculous meningitis. The proteins are elevated with increased cells, mainly lymphocytes, and the glucose is reduced. Goodman, Kaufman and Koenig in 1971 have reported three cases of chronic meningitis which had repeated negative cultures for *C. neoformans* but in which cryptococcal antigen was detected in the C.S.F. by the latex agglutination test. This shows that failure to detect the organism in the C.S.F. does not rule out cryptococcal infection.

The first reported case of Cryptococcal meningitis in Singapore was in 1948 and thereafter from 1959-1970, 30 proven cases have been reported (Tay Chew and Lam 1972) of which 5 cases were in 1968 and 6 cases in 1970. This increase was thought to be apparent, rather than real due to improved laboratory facilities and increased awareness of the disease. During the past two years 21 cases have occurred, 12 in 1974 and 9 cases in 1975 showing that there has been an increase in incidence.

Cryptococcus neoformans was isolated from the C.S.F. from all 21 cases by the following laboratory procedures.

LABORATORY DIAGNOSIS

The C.S.F. received from these patients were clear or opalescent never turbid. The C.S.F. was centrifuged and wet films were made with Indian ink. A drop of the sediment from the centrifuged C.S.F. was mixed with an equal volume of Indian ink and examined under the microscope. The organisms were found to have definite capsules around them, this being a characteristic of *Cryptococcus neoformans*. This organism is the only encapsulated fungus which invades the central nervous system.

Gram stained smears examined under the microscope showed bluish black cells which were oval or round. Most of them were single and rarely showed budding. The centrifuged specimens were inoculated on to chocolate agar plates and sabraud agar, growth was slow and after 24 to 48 hours the colonies were pin point and off white in colour. The colonies could be mistaken for micrococci. A gram stain showed typical budding yeasts, like all other yeasts attached to the mother cell by a narrow neck. A mount with Indian ink showed the capsulated yeast cells. All plates which did not show any growth were re-incubated for a further period at 37 degrees and re-examined for any growth.

Unlike other yeasts *Cryptococcus neoformans* does not produce pseudomycelia and owing to the

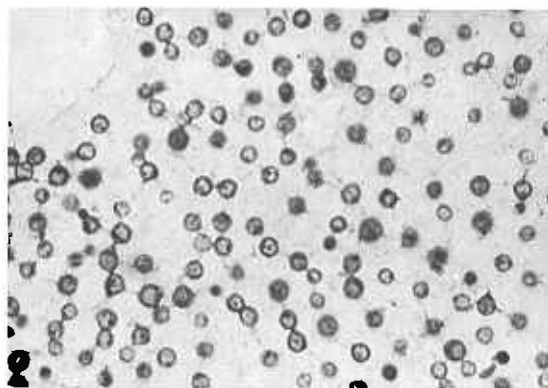


Fig. 1. A gram stained film from a Sabraud agar culture showing budding *Cryptococci neoformans* $\times 500$.

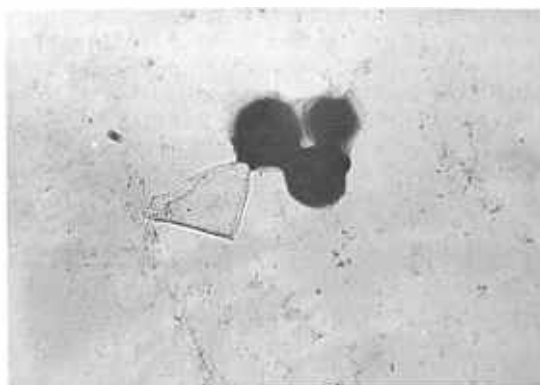


Fig. 2. A gram stained film from a centrifuged deposit of cerebrospinal fluid showing capsulated *Cryptococci neoformans* $\times 500$.

presence of urease it hydrolyses urea in Christensens agar. Blood from only one patient was cultured and *cryptococcus neoformans* was isolated.

The laboratory findings were that all 21 specimens were positive for *Cryptococci neoformans* in both smear and culture.

CLINICAL HISTORY

Most of the patients presented with clinical signs of meningitis. A short history of two of the cases which presented with neurological signs are given below.

The first case was a male 57 years of age who was admitted to medical unit with Jacksonian fits. As there was an abnormality in his E.E.G. he was transferred to the neurological unit.

At the N.S.U. the angiogram did not show any abnormality. As he had a raised intracranial pressure lumbar puncture was not done. Chest X-ray showed a patch of consolidation and the Mantoux test was positive. Subsequently the patient developed neck stiffness and a diagnosis of tuberculous meningitis was made. A lumbar puncture was done.

The C.S.F. smear and culture showed *C. neoformans*. This patient died and at postmortem cryptococcal granulomas were found on the meninges and in the brain.

The second patient was a male 27 years old who presented with neurological signs. He had ptosis and difficulty in moving his eyeballs upwards. A third ventricular tumour was diagnosed. Angiogram was normal. A lumbar puncture was done and the C.S.F. smear and culture were positive for *C. neoformans*.

DISCUSSION

Twenty-one cases of cryptococcal meningitis have been reported during the past two years, 12 in 1974 and 9 cases in 1975. From the figures available in our local literature, 30 cases have been reported during a period of 11 years. The highest number of cases reported during this period was 6 cases in 1970. This shows that there has been an increased incidence of Cryptococcal meningitis in Singapore. Out of the 21 positive specimens received, two specimens were received from the mortuary and the diagnosis of *C. meningitis* was made after the death of the patients.

Seventeen out of the 21 cases were within the age group 20-30 years. Though *C. meningitis* is rare prior to puberty, two of the patients were 7 and 10 years old. Most patients presented with a clinical history suggestive of meningitis except for two cases. One was diagnosed as a case of 3 third ventricular tumour and the other as a case of epilepsy with Jacksonian fits. In both patients the C.S.F. smear and cultures were positive for *C. neoformans*. Blood was received from only one of the patients and *C. neoformans* was isolated, and this case turned out to be fatal. In heavy infection the organism can be isolated from blood, sputum and even from the urine of the patient. Cryptococcal meningitis constitutes 23.7% of fungal and pyogenic meningitis reported by the bacteriology laboratory during the past two years. Hence it is important to bear in mind that when meningitis is diagnosed in a patient the etiology could be a fungal infection.

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REFERENCES

1. Charles A., Carlton M.D., Lester A. and Mount M.D.J.: "Neurosurgical aspects of cryptococcosis." *J. neurosurgery* Vol. 8, 143, 1951.
2. Littman M.L. and Walter J.E.: "Cryptococcosis current status." *Amer. J. Med.* Vol. 45, 922, 1968.

3. Goodman J.S., Kauffman L. and Koenig M.G.: "Serological Tests in the diagnosis of Cryptococcosis." *New England J. Med.* Vol. 285, 434, 1971.
 4. Supramaniam J.M.J., Ng Kwok Choy and Thambyah J.: "Cryptococcosis—A report on three cases with special emphasis on management, a review of the local literature." *Singapore Med. J.* Vol. 10, 153, 1969.
 5. Tay C.H., Chew W.L.S. and Lam L.C.Y.: "Cryptococcal meningitis its apparent increase incidence in the Far East." *Brain* Vol. 95, 825, 1972.
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