

## Two cases of cryptococcosis

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**SYNOPSIS** Two cases of *Cryptococcus neoformans* infection are described, both complicating chronic renal failure. In one case the use of prednisone and immunosuppressive drugs may have predisposed to infection.

Cryptococcosis is a relatively uncommon disease, due to infection with the yeast-like fungus *Cryptococcus neoformans*. The fungus has a world-wide distribution and is found in the soil as a saprophyte, from which it was first isolated by Emmons (1951). The excreta of birds provide a medium for its growth and *Cryptococcus neoformans* has been isolated from bird droppings in many parts of the world, including those of the London pigeon (Partridge and Winner, 1965).

It has been suggested that modern drug therapy causes an increased susceptibility to cryptococcal infection. One of the cases recorded below supports this belief and in both cases chronic renal disease may also have predisposed to infection.

### CASE REPORTS

**CASE 1** A man aged 57 years at the time of his death had suffered for eight years from paraplegia as a result of transverse myelitis thought to be due to herpes zoster. At that time he developed retention of urine, and suprapubic drainage was carried out. This was followed by chronic pyelonephritis and later by hypertension and renal failure. The hypertension was treated with methyldopa, serpasil, and ismelin; the pyelonephritis with furadantin and a variety of antibiotics, including streptomycin and chloramphenicol.

On his final admission he was drowsy and confused and there was a recent history of fits. He was febrile (T. 100°F.) and there was slight neck stiffness. Blood pressure was 140/70 mm. Hg, blood urea level 249 mg./100 ml., serum potassium level 4.6 mEq./l., and there were 15,100 white blood cells per c.mm. (93% neutrophils), showing toxic granulation and a shift to the left. A chest radiograph showed segmental collapse or fibrosis in the left lower lobe. Meningitis was suspected but lumbar puncture yielded clear cerebrospinal fluid at a pressure of 100 mm. It contained 56 red cells and 2 lymphocytes per c.mm. (protein 30 mg./100 ml., sugar 60 mg./100 ml., chloride 103 mEq./l.). The Lange colloidal gold reaction was 000000. The Wassermann reaction was negative. No organisms were grown on culture.

Received for publication 5 May 1966.

Ampicillin and streptomycin were given to control the urinary infection and haemodialysis was performed. The blood urea level fell to 128 mg./100 ml., but rose later to 312 mg./100 ml., and he developed partial heart block with the Wenckebach phenomenon. Further haemodialysis was performed, but he died in ventricular fibrillation 12 days after admission.

**Necropsy** The significant findings were as follows: chronic pyelonephritis with bilateral hydro-ureter and hydro-nephrosis; left ventricular hypertrophy; terminal pancreatitis; enlargement of hilar lymph nodes which contained creamy material. The area of pulmonary collapse seen on radiographs was not identified. The brain was macroscopically normal, but the spinal cord was

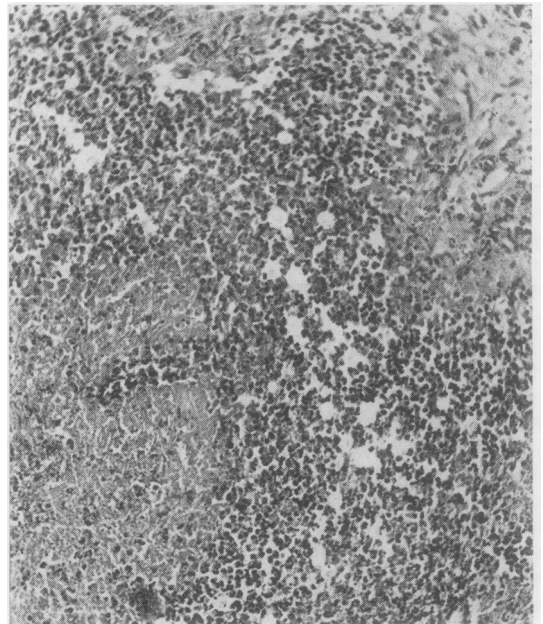


FIG. 1. Necrotic material and polymorphs in a hilar lymph node from case 1. The circular spaces contain cryptococci. Haematoxylin and eosin  $\times 125$ .

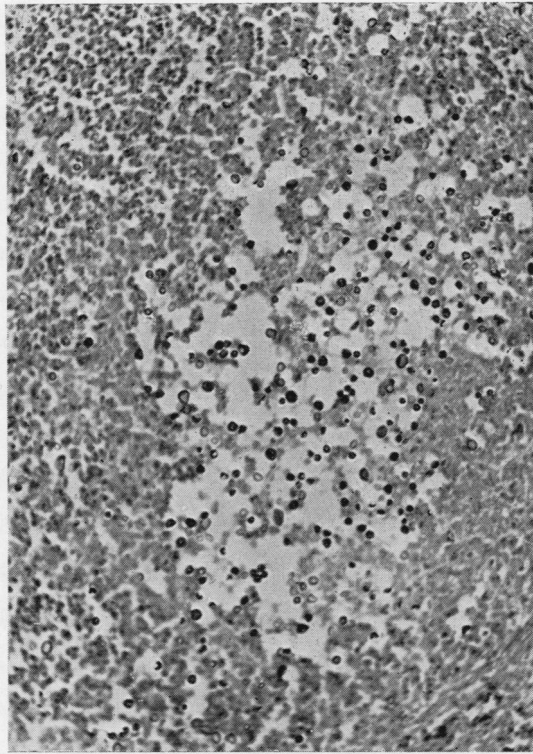


FIG. 2. *Cryptococcus neoformans* in a hilar lymph node (case 1). Gram  $\times 90$ .

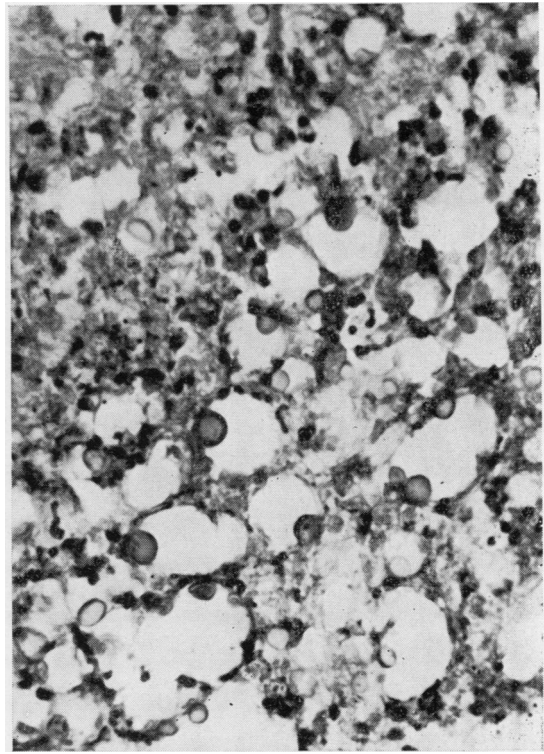


FIG. 3. *Cryptococcus neoformans* in a hilar lymph node (case 1). Mucicarmine  $\times 325$ .

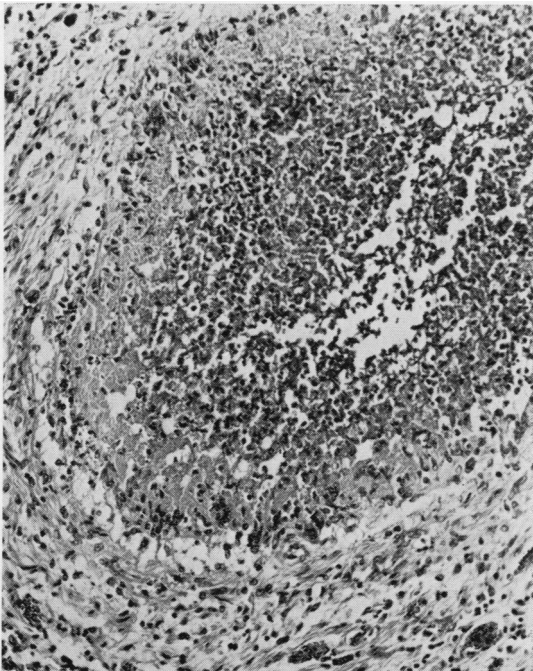


FIG. 4. Histiocytes surrounding an area of suppuration in a hilar lymph node (case 1). Haematoxylin and eosin  $\times 125$ .

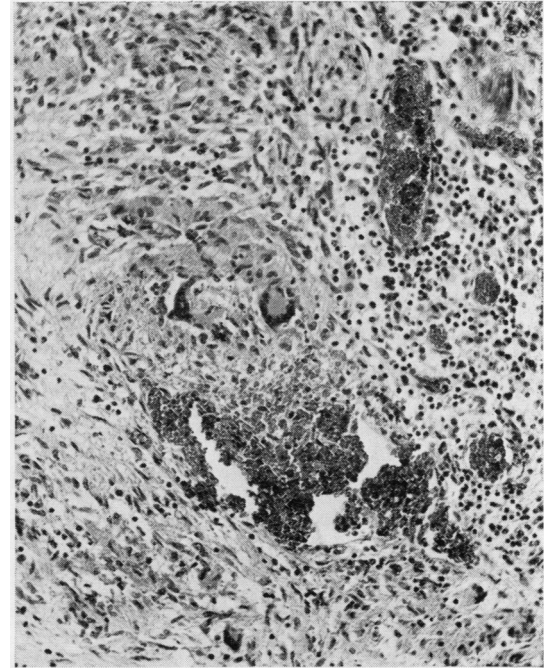


FIG. 5. Giant cells lying at the edge of a granuloma in a hilar lymph node (case 1). Haematoxylin and eosin  $\times 125$ .

narrowed at the level of D12 for a length of 7 mm. A careful examination of the skin of the trunk showed no signs of scarring.

**Histology** The kidneys showed the changes of long-standing pyelonephritis. In the narrowed segment of spinal cord the anterior horns were destroyed with gliosis and thickening of the leptomeninges. The dorsal root ganglia which were examined showed nothing of note.

An unexpected finding was the presence of a fungal infection in the hilar lymph nodes, the kidneys, and possibly the pancreas, although the last mentioned may have been artefact due to contamination of the sections during processing.

The normal architecture of the hilar nodes was destroyed and replaced by widespread necrosis and supuration (Fig. 1). Numerous yeast-like fungi were identified, each surrounded by a clear zone. The largest were about twice the diameter of a red cell. They were Gram-positive, P.A.S.-positive, and had capsules staining strongly with mucicarmine (Figs. 2 and 3). The inflammatory process contained multinucleated giant cells, and the necrotic zones were surrounded by histiocytes in palisade formation (Figs. 4 and 5). Suppurating granulomata containing similar fungi were found in the cortices of the kidneys. No fungi were seen in sections of the affected spinal cord or in the dorsal root ganglia, and the cause of the myelitis remains uncertain.

**CASE 2** A 32-year-old woman in a late stage of chronic glomerulonephritis with renal failure was treated by cadaveric renal homotransplantation followed at once by immunosuppressive therapy. This consisted of imuran (azathiopurine), an imidazolyl thiopurine, 250-400 mg. daily, and actinomycin C intermittently up to 400  $\mu$ g. daily. Other drugs received at this time included penicillin, methicillin, furadantin, orbenin, chloramphenicol, thiosporin, and streptomycin.

Convalescence was stormy, and at one time her white blood cell count fell to 200 per c.mm., and her platelet count to 50,000 per c.mm. She was discharged on imuran, 150 mg. daily, two months after operation.

In the next few months she received further doses of actinomycin C and the imuran was reduced to 50 mg. daily. She was also started on prednisone 45 mg. daily. Prednisone and imuran were then given continuously, although the dose of prednisone was subsequently reduced to 5 mg. daily. Hypertension was controlled with methyldopa and aldomet and she received a variety of antibiotics at various times before her death, which occurred two years and five months after her operation.

For the last 12 months her blood urea level varied between 150 and 200 mg./100 ml. and the white blood cell count remained normal. She was finally admitted in congestive heart failure with bilateral pleural effusions, complaining of chest pain and paroxysmal dyspnoea, and died soon afterwards from pulmonary oedema.

**Necropsy** The relevant findings were left ventricular hypertrophy and pulmonary oedema; plural effusions; ascites and oedema of the legs.

**Histology** Multiple granulomata containing cryptococci were found in the lungs, spleen, transplanted kidney, and the patient's own kidneys. These consisted of clusters

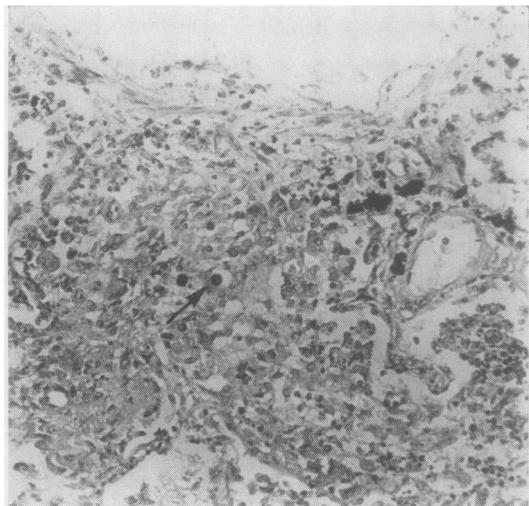


FIG. 6. Non-suppurating granuloma, containing cryptococci (arrow), in the lung lying close to the wall of a vein (case 2). Gram  $\times$  120.

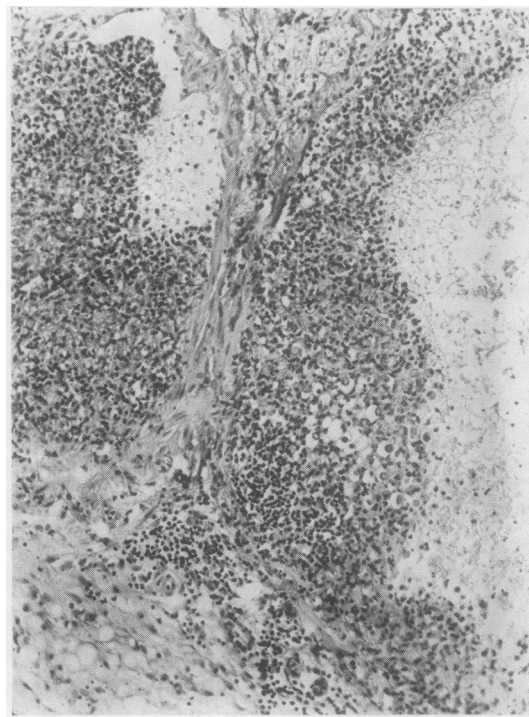


FIG. 7. Vessels in the mediastinal tissue filled with granulation tissue containing cryptococci (case 2). Mucicarmine  $\times$  70.

of histiocytes and poorly formed giant cells, with no necrosis and little surrounding inflammation. In the lungs some of the granulomata lay close to the walls of veins and lymphatics (Fig. 6).

In the thymus, anterior mediastinal and iliac lymph nodes, there were large suppurating granulomata similar to those in case 1. Many of the lymphatics or veins in the mediastinal tissue were filled with granulation tissue containing cryptococci (Fig. 7). No organisms were found in the brain.

In both these cases fungal infection was unsuspected and noted only during examination of post-mortem tissue sections. The identity of the organism must thus rest on its highly characteristic morphology and staining reactions. The spherical or ovoid bodies, each surrounded by a clear zone (due to shrinkage of the capsule during processing), are typical of the organism, and the intense mucicarmine staining of the acid mucopolysaccharide in the capsule is peculiar to this type of yeast-like fungus (Littman and Zimmerman, 1956).

#### DISCUSSION

Cryptococcosis has only rarely been reported in the United Kingdom. Rook and Woods (1962) were able to collect 21 cases from the British literature, adding a case of cutaneous cryptococcosis of their own. More recently Rippey, Roper, Jeanes, and Bright (1965) described a case of cryptococcal meningoencephalitis.

The portal of entry is usually the lungs, through which dissemination may occur to other parts of the body, especially the meninges, and *Cryptococcus neoformans* is the commonest cause of mycotic meningitis. Infection is often primary but may complicate some underlying disease, particularly leukaemia and malignant disease of the lymphoreticular system (Zimmerman and Rappaport, 1954).

The characteristic lesion is a non-suppurating granuloma, but a caseous appearance is sometimes produced by widespread death of cryptococci, possibly due to development of hypersensitivity (Baker and Haugen, 1955). Extensive necrosis and suppuration such as occurred in these two cases is most uncommon.

Involvement of mediastinal glands must be unusual as it is not mentioned in the series of 12 cases of pulmonary cryptococcosis by Haugen and Baker (1954).

In the two cases described, cryptococcal infection appears to have been no more than a contributory cause of death, and cryptococcal granulomata have been previously described in the lungs of patients dying of other diseases (Haugen and Baker, 1954).

The common opportunistic fungi are candida,

mucor and aspergillus, and infection following the administration of anti-leukaemic drugs, immunosuppressives, steroids, and antibiotics is well documented (Keye and Magee, 1956; Torack, 1957; Baker, 1965). Cryptococcosis is less commonly drug induced (Baker, 1965; Symmers, 1964), but some authors believe that modern therapy results in an increased susceptibility to infection (Keye and Magee, 1956; Goldstein and Rambo, 1962).

Opportunistic infection has been an important complication following renal transplantation: candidiasis, aspergillosis, and infection with *Pneumocystis carinii* and cytomegalic inclusion virus are described by Rifkind (1964) and cryptococcal meningitis by Murray, Gleason, and Bartholomay (1965).

Baker (1965) mentions renal disease as a factor predisposing to fungal infections and it has long been known that chronic uraemia depresses the immune mechanism of the body (Dammin, Couch, and Murray, 1957).

In both cases described, chronic uraemia may have predisposed to infection, but it seems reasonable to suggest that in case 2 the administration of prednisone and the immunosuppressives, imuran and actinomycin C, also predisposed to cryptococcal infection or to the activation of a latent focus. If this is so, the prednisone and imuran were probably more important, since they were given continuously.

The only effective drug meantime available for treatment is amphotericin B, which may arrest the progress of the disease; but relapses are common, and the drug has important toxic effects (Rippey *et al.*, 1965).

Solitary pulmonary lesions have been successfully resected (Dillon and Sealy, 1962; Houk and Moser, 1965). In such cases culture of the sputum or examination of indian ink preparations may be valuable aids to diagnosis.

I wish to thank Professors M. D. Milne and R. Y. Calne for permission to publish these cases, and Professor A.D. Morgan for his valuable help. My special thanks are due to Professor W. St. C. Symmers for identifying the fungus in both cases. Finally I am grateful to the Department of Medical Photography, Westminster Medical School, for the photomicrographs.

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