Cryptococcal Meningitis

A CASE TREATED WITH 5-FLUOROCYTOSINE

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SUMMARY

Cryptococcal meningitis occurred in an elderly Coloured woman in the Northern Cape. She presented with symptoms and signs suggestive of encephalitis 4 weeks after a cholecystectomy. After the administration of cortisone, cryptococcal organisms were isolated in her cerebrospinal fluid. She was first treated with intravenous amphotericin-B without improvement, and then with 5-fluorocytosine orally, to which she responded without appreciable side-effects. An abdominal gland biopsy suggested sarcoidosis, but sarcoid reaction may occur in the presence of cryptococcosis, although the organisms could not be demonstrated, as is often the case.

S. Afr. Med. J., **48**, 555 (1974).

CASE HISTORY

A 65-year-old Coloured woman had been complaining of intermittent nausea and vomiting, with no relation to meals, for more than a year. On examination in July 1972 she was found to have mobile glands in the left supraclavicular fossa, both axillae and both groins. Her liver was palpable with a firm regular edge.

Investigations

Her haemoglobin level was 14,1 g/100 ml; white cell count 5 000/mm^3; erythrocyte sedimentation rate 6 mm/hour (Westergren). The radiograph of the chest was normal. A cholecystogram demonstrated a non-functioning gall bladder. At laparotomy gall stones were found, as well as large fleshy glands around the porta hepatis and along the lesser curvature of the stomach. A biopsy specimen was taken and the histology was reported to show non-specific inflammatory changes. Her postoperative recovery was uneventful.

Four weeks later the patient presented at another hospital with severe headache, mild neck stiffness and fever. A lumbar puncture showed protein 80 mg/100 ml; sugar 80 mg/100 ml; lymphocytes 4/mm^3; polymorphs 1/mm^3; chlorides 670 mg/100 ml. A diagnosis of encephalitis was made and with the persistence of symptoms, cortisone was added to her treatment. A repeat lumbar puncture was performed after a worsening of her clinical condition, with the following results: protein 300 mg/100 ml; polymorphs 23/mm^3; lymphocytes 6/mm^3; sugar nil; chlorides 650 mg/100 ml. Her cerebrospinal fluid pressure was raised at this stage.

She was transferred to Kimberely Hospital in September 1972. Her complaints were severe headache, weakness of all limbs, and pain in her neck. On examination she was mentally depressed with neck stiffness, and reflexes were generally decreased, but there were no localising signs nor nerve involvement. No papilloedema was present and the chest and rest of the examination were normal. Her temperature was 38°C.

Further Investigations

A lumbar puncture showed a raised cerebrospinal fluid pressure, protein 295 mg/100 ml; sugar 29,5 mg/100 ml; chlorides 670 mg/100 ml; polymorphs 400/mm^3; lymphocytes 125/mm^3; erythrocytes 100/mm^3. On direct microscopy of the cerebrospinal fluid, encapsulated yeast cells resembling *Cryptococcus neoformans* were seen, and confirmed with India ink stain and on culture. Further investigations were as follows: haemoglobin 14,8 g/100 ml; white cell count 15 200/mm^3; erythrocyte sedimentation rate 31 mm/h (Westergren): urea 33 mg/100 ml; uric acid 3,9 mg/100 ml; creatinine 0,9 mg/100 ml; electrolytes: potassium 3,9 mEq/litre; sodium 136 mEq/litre; chlorides 102 mEq/litre; blood sugar 90 mg/100 ml; serum calcium 11 mg/100 ml.

An infusion of amphotericin-B was started. She remained acutely ill without change in pyrexia or clinical condition and, after 10 days, treatment was commenced with 5-fluorocytosine as a supply of this drug had become available. Her temperature was normal within 5 days and a repeat lumbar puncture showed protein 175 mg/100 ml; sugar 40 mg/100 ml; chlorides 720 mg/100 ml; polymorphs 26/mm^3; lymphocytes 289/mm^3. After 2 weeks she was asymptomatic. On review of the histology of the previous abdominal gland biopsy, a diagnosis of sarcoidosis was made. The cerebrospinal fluid returned virtually to normal within 6 weeks, and 6 months after completion of treatment she remained well with normal cerebrospinal fluid values (Fig. 1).

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Date received: 7 September 1973.

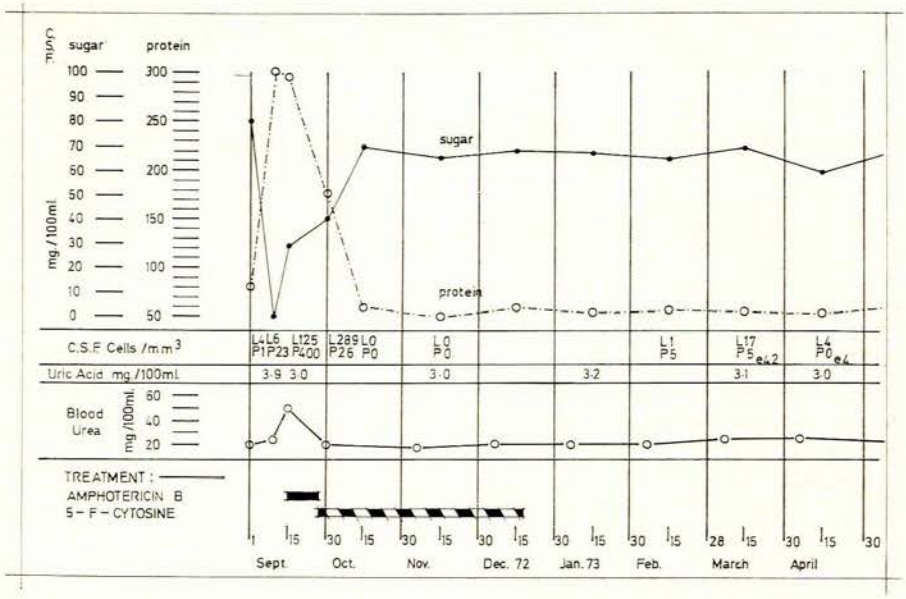

Fig. 1. Chart of laboratory findings and therapy, including cerebrospinal fluid, cell counts (L = lymphocytes; P = polymorphs, e = erythrocytes), blood urea, uric acid, and periods of treatment with amphotericin-B and 5-fluorocytosine.

DISCUSSION

Cryptococcosis is a highly fatal infection caused by *Cryptococcus neoformans*, an encapsulated yeast with a special predilection for the central nervous system. The possibility of underlying Hodgkin's disease, lymphosarcoma, leukemia or diabetes should be considered in every patient with cryptococcosis, as it occurs with increased frequency in such patients.[1] The granulomatous inflammatory reaction produced by *Cryptococcus neoformans*, especially in the lymph nodes and bone, may contain typical non-caseating tubercles just as are seen in the sarcoid reaction. When the organisms cannot be identified, as is often the case in tissue sections, it may be impossible to distinguish between the two diseases.[2] Boeck's sarcoidosis and cryptococcosis seldom coexist.[3,4] The demonstration of a sarcoid reaction in our patient's gland biopsy is most probably due to *Cryptococcus neoformans*, although organisms were not demonstrated on histology. It seems probable that isolation of *C. neoformans* after steroid therapy was due to an exacerbation as a result of the cortisone therapy. In the Mississippi Valley, where torulosis is endemic, hydrocortisone (100 mg intravenously) is used as a provocative test in cases of obscure chronic meningitis.[5]

Until 1957 there was no successful treatment for most cases of cryptococcosis. Cryptococcal meningitis was almost always fatal. The introduction of amphotericin-B reduced the mortality of cryptococcal meningitis from above 90% in the first year to 25% over 3 years. Intravenous administration (up to 1 mg/kg/day until 3 g is given) and intrathecal administration (0,025 mg increasing to 0,5 mg daily) are recommended. Severe side-effects may occur including idiosyncratic reactions and impaired renal function. The latter occurs in 80% of treated cases although permanent renal damage can usually be prevented by reducing the dose.[6] In this patient, amphotericin-B was discontinued after 10 days as she showed no response to intravenous administration.

5-Fluorocytosine represents an important advance in the chemotherapy of cryptococcosis and some serious fungal diseases, especially systemic moniliasis.[7] 5-Fluorocytosine is reported to be an antimetabolite of cytosine in *C. neoformans*, *Candida albicans* and other fungi, but apparently not in man. It is effective in reducing growth in these fungi but has no antibacterial effect.[8] 5-Fluorocytosine is administered orally in a dose of 200 mg/kg/day in 4 divided doses and continued for 6 weeks. After this period the maintenance dose should be 100 mg/kg/day.[8] The drug is excreted mainly by the kidneys and has a wide margin of safety; potentially toxic high plasma levels follow normal dosage regimens in patients with renal insufficiency. The drug is distributed widely in the body and not bound to plasma proteins. Evidence was obtained that 5-fluorocytosine is excreted by filtration at glomerular level without significant tubular reabsorption or secretion. No evidence was obtained that 5-fluorocytosine is deaminated to 5-fluoro-uracil after administration by this route. Cerebrospinal fluid concentration of the drug is almost equal to blood levels.[7]

We wish to thank Roche Products (Pty) Ltd. for data and the supply of 5-fluorocytosine.

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