A Case of Cryptococcosis treated with 5-fluorocytosine

Soo Hyung Kim and Duk Jin Yun

Department of Pediatrics, Yonsei University College of Medicine,
Seoul, Korea

Tai Seung Kim

Department of Pathology, Yonsei University College of Medicine,
Seoul, Korea

SUMMARY

A patient, treated for systemic cryptococcal infection with 5-fluorocytosine, an antifungal agent effective in experimental infection with Candida and Cryptococci, exhibited a satisfactory clinical response from therapy. A systemic infection, caused by Cryptococcus neoformans, was confirmed in this case by skin and liver biopsies and cultures. Cerebrospinal fluid also showed yeast-like budding cells on wet India ink preparation with a positive culture of cryptococci.

The treatment of systemic cryptococcal infection recently was done experimentally with a new agent, 5-fluorocytosine, which is effective in Cryptococcus neoformans, Candida albicans and other fungi as an antimetabolite of cytosine in these fungi, but has no antibacterial effect (Holt and Newman, 1973). Cryptococcus neoformans, non-mycelial budding yeast, is unique among the fungi in that it produces a mucinous capsule which is periodic acid-Shiff-stain positive (Lewis and Rabinovich, 1972). The organism was first isolated about 1895 from a gumma-like lesion of the tibia of a patient by Busche (1895) and Busse (1894). Verse (1914) in 1914 reported the first case of meningitis associated with Cryptococcus neoformans infection. The meningial type of the disease is the best known form, and the most frequently involved organ system is the central nervous system, but the organism has been found in almost all other organ systems including the kidney, heart, spleen, pancreas, adrenals, ovaries, lymphnodes, skeletal muscle, liver, gastrointestinal tract and skin (Littman and Zimmerman, 1966; Campbell, 1966; Linden and Steffen, 1964; Cawley et al, 1950; Collins, 1950; Rawson et al, 1948; Bowman and Ritchey, 1954; Sabesin et al, 1963; Procknow, et al, 1965; Gollan et al, 1972; Randall et al, 1968; Tillotson and Lerner, 1965). Until 1967, there was no successful treatment for most cases of cryptococcosis. Cryptococcal meningitis was almost always fatal even with roentgen therapy, sulfonamide, diamidines, iodides, penicillin, tetracycline, ethyl vanilate, nystatin and cycloheximide (Emanuel et al, 1961). The introduction of treatment with amphotericin B reduced the mortality of cryptococcal meningitis from about 90% to 25% over 3 years (Van den Ende et
al, 1974). The following is the case history of the patient whom we treated successfully with 5-fluorocytosine.

**REPORT OF A CASE**

The patient was a 39-month old girl, who had been relatively healthy 4 months previously. She was admitted to the Pediatric Department of Severance Hospital on May 8, 1975, with the chief complaints of abdominal distention and palpable hard masses in both upper abdominal quadrants, jaundice and numerous skin patches with oozing and crusts on the entire body, especially on the face and extremities, of 4 months duration. Before admission, she had been treated at other hospitals under the diagnosis of liver cirrhosis with findings of jaundice and hepatosplenomegaly. Fifteen days prior to admission, frequent voiding was noticed by her parents.

On admission, the vital signs were: pulse rate 140/min., respiration rate 36/min., blood pressure 105/60 mmHg., and body temperature 37.2°C. She was a little small for her age and her mentality was clear. She appeared to be

![Fig. 1. Pin-head to pea-sized, scaly, erythematous, hard patches with crust formation and varioliform scars. Marked hepatosplenomegaly is also noted.](image)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>1975</th>
<th>1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (Kg.)</td>
<td>13.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Lymphnode swelling</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>Crytococcus demonstrated</td>
<td>14.8</td>
<td>14.8</td>
</tr>
<tr>
<td>Pus from skin lesion</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphnode biopsy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Stool</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Urine</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>C. S. F.</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hgb. (gm/dl)</th>
<th>9.4</th>
<th>8.8</th>
<th>8.2</th>
<th>9.4</th>
<th>9.5</th>
<th>11.7</th>
<th>13.4</th>
<th>13.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (x 10³)</td>
<td>346</td>
<td>276</td>
<td>226</td>
<td>214</td>
<td>117</td>
<td>7</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>47</td>
<td>34</td>
<td>30</td>
<td>35</td>
<td>7</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. S. R. (mm/hr)</td>
<td>138</td>
<td>70</td>
<td>72</td>
<td>68</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Direct (mg/dl)</td>
<td>70</td>
<td>95</td>
<td>38</td>
<td>3.0</td>
<td>0.9</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin/Globulin (g/dl)</td>
<td>3.1/4.2</td>
<td>9.2/4.4</td>
<td>9.4/4.5</td>
<td>9.3/4.5</td>
<td>9.0/3.8</td>
<td>44/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>6.0</td>
<td>5.8</td>
<td>5.6</td>
<td>5.0</td>
<td>4.9</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (S.U.)</td>
<td>5.0</td>
<td>6.5</td>
<td>6.0</td>
<td>5.0</td>
<td>4.9</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. G. P. T. (Unit)</td>
<td>16.8</td>
<td>15.4</td>
<td>12.8</td>
<td>12.8</td>
<td>12.8</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porthrombin time(sec % of normal)</td>
<td>52</td>
<td>69</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Prednisolone | | |
| 5-fluorocytosine | | |

Fig. 2. Symptoms and course of the case.
chronically ill. Her skin was generally jaundiced. There were pin-head to pea sized slightly scaly erythematous hard patches with crust formation and varioliform scars on the whole body, especially on the face and extremities. Numerous hard, movable, various-sized lymph nodes were palpated in the cervical, axillary and inguinal regions. Sclerae were icteric and conjunctiva were a little pale. Neck rigidity was negative. Breathing sounds were coarse over both lung fields. The liver was palpable 6 cm. below the right costal margin and had a hard consistency, smooth surface and sharp edge. The spleen was also palpable 6 cm. below the left costal margin, and was firm. Shifting dullness was present together with marked abdominal distention(Fig. 1).

Symptoms, hospital course and laboratory findings are illustrated in Fig. 2. Laboratory findings in the active phase showed leukocytosis with a marked eosinophilia, increased erythrocyte sedimentation rates, increased bilirubin level including direct bilirubin, an elevated alkaline phosphatase level and prolonged prothrombin time. The first skin biopsy performed on the second hospital day disclosed cryptococcal infection(Fig. 3). Cerebrospinal fluid also showed encapsulated budding yeast cells on the wet India ink preparation(Fig. 4). A liver biopsy was done on the 7th hospital day because of poor liver function(Fig. 2), and this also showed cryptococci with granulomatous inflammation and cholestasis and the culture grew cryptococci on Sabouraud’s media(Fig. 5). Chest X-ray on admission revealed mottled densities in both upper and lower lung fields without increased vascular markings or hilar adenopathies(Fig. 6). A liver scan and a bone marrow aspiration were performed on admission with no abnormal findings.
Fig. 6. P-A Chest X-ray on admission. Disseminated mottled densities in entire lung fields.

An infusion of amphotericin B was started with a dose of 1.0 mg./kg./day and with the amount increased to 3.0 mg./kg./day beginning on the 2nd day. Because of the side effects of severe abdominal pain and high fever (39.0 C), medication was changed to 5-fluorocytosine. At first, 100 mg./kg./day was given after evaluations of kidney function, blood urea nitrogen, creatinine and creatinine clearance. On the 20th day of admission, the amount was increased to 150 mg./kg./day after re-evaluation of kidney function. Urinary infection occurred, caused by Escherichia coli with more than 100,000/ml. by colony count. Kanamycin was given for the infection, combined with 5-fluorocytosine, with good results. The second liver biopsy done on the 33rd hospital day revealed a decreased number of cryptococci and decreased granulomatous inflammation and cholestasis. On the 36th hospital day, she was discharged and continued on medication.

She was happy and felt well after discharge. Since repeated skin biopsies showed cryptococci, the dose of 5-fluorocytosine was increased to 280 mg./kg./day after checking the kidney function. This dosage is almost double the recommended maximal dose. This large dose was given at first with prednisolone 1 mg./kg. daily for one month with the hope of earlier healing and the large dose was continued for more than 6 months until the last skin biopsy showed no cryptococci. This large dose of 5-fluorocytosine did not cause any untoward effects.

**DISCUSSION**

Because of the rarity of cryptococcosis or cryptococcal meningitis in every country, making the diagnosis is not so easy. For 4 months, several other hospitals treated this case as liver cirrhosis and gave a guarded prognosis. The laboratory diagnosis of cryptococcosis usually depends on the microscopic demonstration and culture of the organism (Fetter et al, 1969). Until recently, serologic tests for the diagnosis of cryptococcosis have met with little success, but Broomfield et al. (1963) described a method of sensitizing latex particles with globulins from rabbits injected with Cryptococcus neoformans. These particles were then used in agglutination tests in body fluid. Further experiences with this test were described by Gorden and Vedder (1966), who also showed that direct agglutination of specimens of Cryptococcus neoformans was an effective way of detecting antibodies. More recently, a combination of agglutination and a complement fixation test has been reported on favorably by Walter and Jones (1968). The final diagnosis is usually performed after biopsy and culture.

Clinical symptoms are correlated with the organs infected by the organisms. Symptoms and signs of central nervous system involvement are headache followed by nausea and vomiting, disturbances of consciousness and
A Case of Cryptococcosis treated with 5-fluorocytosine

orientation, meningeal signs, cranial nerve involvement and pathologic reflexes. However in this case there were no signs of meningeal and central nervous system involvement even though the cerebrospinal fluid contained Cryptococcus neoformans. A significant percentage of patients with pulmonary cryptococcosis had no respiratory symptoms or signs, as in our case. Usual respiratory symptoms of cryptococcosis include cough and shortness of breath (Campbell, 1966).

Amphotericin B can be given only by the intravenous route and may have severe side effects such as fever, chills, vomiting, and phlebitis (Emanuel et al., 1961; Van den Ende et al., 1974; Littman et al., 1968) even in low dosages and most important, apart from idiosyncratic reactions, impaired renal function (Gordon and Vedder, 1966; Smith and Matthews, 1960; Winn, 1959). This occurs in 80% of treated cases, though permanent renal damage usually can be prevented by reducing the dose (Bell et al., 1962). The drug gave rise, in our case, to several well-recognized and severe side effects including high fever and abdominal pain which necessitated withdrawal of the drug after only 7 mg. had been given. Moreover, the patient had urinary tract infection with Escherichia coli. We have had 7 cases of cryptococcal meningitis in our department during the last 15 years. Amphotericin B was given to all of them and 6 died. One has ultimately survived (Lim, 1965). Therefore, we are concerned about the effects of amphotericin B, despite the good results noted in the literature.

5-fluorocytosine has been tried in the treatment of cryptococcal meningitis in the U.S.A. (Grunberg et al., 1967). It can be given by the oral route and is reported to be an antimetabolite of cytosine in Cryptococcus neoformans, Candida albicans and other fungi, but apparently not in man. It is effective in inhibiting the growth of these fungi (Watking et al., 1969). Fungistatic concentration persists in the blood for 6 to 10 hours after a single oral dose of 2 gm. of 5-fluorocytosine in man. It is excreted mainly by the kidneys and has a wide margin of safety. A case of reversible pancytopenia after 4 weeks of treatment with 5-fluorocytosine was reported by Tassel and Madoff (1968) and a transient rise in serum transaminases occurred in one previous patient. The cerebrospinal fluid concentrations of the drug were almost equal to the blood level (Watkins et al., 1969). Tassel and Madoff (1968) reported a case resistant to treatment with 5-fluorocytosine in a dose of 2.25 gm./day for 50 days. In our patient, cerebrospinal fluid showed no yeast cells 10 days after medication. Thirty days after initiating treatment, decreased cryptococci in the skin biopsy and a decrease in the size and hardness of the liver and spleen were noticed. After 2 months of treatment with maximal recommended dose of 5-fluorocytosine (150 mg./kg./day), this dose was extended for another 6 months. There were no side effects with this large dose which resulted finally in complete healing. With the advantage of the oral administration route and many fewer side effects, 5-fluorocytosine may well replace amphotericin B as the chosen treatment for cryptococcosis, but further trials are recommended.

REFERENCES

1968.


1976

A Case of Cryptococcosis treated with 5-fluorocytosine


