Cerebral candidiasis: case report of brain abscess secondary to *Candida albicans*, and review of literature

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**Summary**  A patient with a brain abscess due to *Candida albicans* is reported. This patient had three episodes of systemic candidiasis in spite of the fact that she had no underlying debilitating disease and had never received prior antibiotic or adrenocortical steroid therapy. A review of the literature reveals 42 cases of central nervous system *Candida albicans* infection. The salient features of these cases are tabulated and discussed. The clinical features, pathology, pathogenesis, treatment, and aetiology of cerebral candidiasis are also discussed.

*Candida* organisms are common saprophytes which reside on the skin and mucous membranes of the gastrointestinal tract in healthy persons, and in the vagina of pregnant and diabetic women. This fungus is ordinarily a weak pathogen which produces mild superficial infection, but occasionally it may cause a systemic disease with involvement of the lung, kidney, endocardium, brain, or reticuloendothelial system. In almost all instances of acute disseminated candidiasis the defence mechanisms of the host have been reduced by predisposing factors such as prior antibiotic therapy (Seelig, 1966), systemic adrenocortical steroids (Louria, Stiff, and Bennett, 1962), indwelling intravascular catheters (Louria et al., 1962), diabetes mellitus, and other serious chronic diseases. In addition, various neoplastic diseases such as lymphoma and Hodgkin’s disease (Casazza, Duvall, and Carbone, 1966) favour the development of Candida infection and dissemination, but even in these diseases the development of systemic candidiasis was a rare event before modern therapy with bone marrow suppressants, antibiotics, steroids, and roentgen irradiation (Friedman, 1965).

A case report is presented of a patient afflicted with three episodes of systemic *Candida albicans* infection, the last of which primarily involved her central nervous system. All three episodes occurred without underlying debilitating disease and without prior antibacterial or hormonal therapy. Previous reports of *Candida albicans* infection of the central nervous system are reviewed. In addition, the pathology, pathogenesis, treatment, aetiology, and clinical aspects of this and the other reported cases are discussed.

**Case Report**

The patient was a 29 year old French Canadian woman who was in good health until September 1965 when she developed cervical lymphadenopathy. In November 1965 a cervical lymph node biopsy revealed *Candida albicans* for which she received approximately 1 g intravenous amphotericin B. She did well until May 1967 when she developed vaginal moniliasis, generalized lymphadenopathy, and an abdominal mass. A large abdominal lymph node was biopsied during exploratory laparotomy and amphotericin B was reinstalled after culture revealed *Candida albicans*. She received a total of 1425 g amphotericin and by October 1967 she had no clinical evidence of the disease.

The patient had been pregnant four times during which she never developed vaginal moniliasis. A review of the family history revealed that none of her family had frequent or bizarre infections.

In August 1968 she was seen for the first time by the author. She was two months pregnant but otherwise asymptomatic. Physical examination, radiographs of the chest, and liver function tests were normal.

On 5 February 1969 the patient had a grand mal seizure and physical examination one hour later revealed her to be disorientated and somnolent. A uterus consistent with a 8½ month pregnancy was felt on abdominal examination, but vaginal moniliasis was not present. The remainder of the physical examination disclosed no abnormalities. Laboratory data including haematocrit, haemoglobin, total and differential white blood count,
urinalysis, serum electrolytes, calcium, phosphorus, blood urea nitrogen, liver function tests, and five hour glucose tolerance test were normal. A lumbar puncture showed an initial pressure of 120 mm Hg with a cell count of 1 lymphocyte/c. mm, and glucose content of 56 mg/100 ml. No fungus or bacteria grew in the cerebrospinal fluid cultures. An electroencephalogram was normal. No other neurological procedures were attempted because of the patient's pregnancy. Several days after admission she delivered a healthy, 6 lb. 7 oz. (2-9 kg) female child who had no evident vaginal or cutaneous moniliasis.

On 6 March 1969, the patient developed spontaneous paraesthesias and involuntary clonic movements of the right arm and right side of the face. There was no associated loss of consciousness, although the focal seizure lasted two hours.

PHYSICAL EXAMINATION  The patient was a well-developed well-nourished woman with a normal blood pressure and pulse rate. Both buccal and vaginal moniliasis were present, but she had no lymphadenopathy, hepatosplenomegally, cardiomegaly, or heart murmurs.

NEUROLOGICAL EXAMINATION  She was anxious but well orientated and cooperative. The pupils were round, equal, and reactive to light. Ophthalmoscopic examination revealed bilateral early papilloedema. Hypalgesia, hyperreflexia, and an extensor plantar response were present on the right side. In addition, there was weakness of the right lower face. Cerebellar function was normal.

LABORATORY DATA  Complete blood count included a haematocrit of 47% and a total leukocyte count of 7,900/cu. mm. The differential white blood count showed 64% neutrophils, 30% lymphocytes, and 6% eosinophils. Urinalysis and stool examinations were normal. Blood chemistry studies including fasting blood sugar, blood urea nitrogen, serum electrolytes, calcium, phosphorus, alkaline phosphatase, sulphobromophthalein (Bromsulfalein) retention, serum glutamic oxalic and pyruvate transaminases and protein bound iodine were normal. Protein electrophoresis and immunoglobulin electrophoresis were also within normal limits. Two blood and urine cultures were negative for fungus and bacteria. Radiographs of the skull and chest were normal. Brain scan with mercury (Fig. 1) showed increased uptake of radioactive isotope in the left postero-parietal region. A ventriculogram showed downward displacement of the roof of the lateral ventricle with a shift of the ventricular system from left to right (Fig. 2). Cerebrospinal fluid taken from the lateral ventricle before the ventriculogram contained 10 lymphocytes and 5 red blood cells/cu. mm, protein of 60 mg/100 ml., and sugar of 40 mg/100 ml. An aspiration biopsy through a left postero-parietal trephine site yielded soft semi-liquified brain tissue. Periodic acid-Schiff (PAS) stains of the biopsy material revealed budding yeast-like organisms along with many granulomas and multinucleated giant cells. Special stains for acid fast bacteria were negative. Cultures of the cerebrospinal fluid and cerebral tissue yielded Candida organisms. The species was subsequently identified as *Candida albicans* by the Communicable Disease Centre in Atlanta, Georgia.

HOSPITAL COURSE  After positive identification of a fungal infection by brain biopsy, intravenous amphotericin B was started with an initial dose of 10 mg and gradually increased to a dose of 30 to 50 mg every other day. By the seventh hospital day she had developed global aphasia and complete right upper extremity paralysis. By the 18th hospital day she had received a total of 430 mg intravenous amphotericin and her blood urea nitrogen had risen to 36 mg/100 ml. An Ommaya reservoir was inserted.
into the right lateral ventricle of the brain to permit
direct injection of amphotericin into the central nervous
system. An initial dose of 1 mg amphotericin was injected
through this reservoir. Several hours later the patient
developed diaphoresis, vomited, and within 12 hours
she was in a deep coma. Throughout the next few days
she showed signs of increasing intracranial pressure
which did not improve with systemic steroid therapy.
She died on the 21st hospital day.

Before her death, the patient’s peripheral white blood
cells were stained with benzidine nitroprusside to
determine the presence of the enzyme myeloperoxidase
(Washburn, 1928). Her neutrophils showed positive
staining for this enzyme.

GENERAL NECROPSY The heart was normal in size and
there was no evidence of valvular disease. The lungs were
unremarkable except for a small area of bronchial
pneumonia and atelectasis, but the hilar lymph nodes
contained several small granulomata. The liver was
normal in size, shape, and consistency but microscopic
sections revealed several small granulomas which
contained positive PAS staining fungal organisms. The
spleen weighed 310 g and contained multiple small, soft
granulomata 1 to 4 mm in diameter in which PAS positive
fungal organisms were demonstrated. The kidneys were
of normal size but were soft in consistency. Microscopic
examination showed embolized fungi in the glomeruli.
There was no evidence of fungi on both gross and
microscopic examination of the gastrointestinal tract.

NEUROPATHOLOGICAL FINDINGS The brain weighed
1,130 g and was oedematous and hyperaemic throughout.
An exudate was present over the convexity and base of
the brain and covered the pituitary. The blood vessels at
the base of the brain were of normal calibre and were
free of atheroma. Within the left parietal region a large
fluctuant mass could be palpated but was not visible on
the surface of the cortex. The convolutions of the left
cerebral hemisphere, particularly in the left parietal
region, were widened and the fissures were small. The
cerebellar tonsils were herniated and there was notching
of the hippocampal gyri bilaterally.

Horizontal sections through the cerebral hemispheres
revealed a large ill-defined, soft mass 8 cm in diameter,
in the left mid and posterior parietal region. The mass
was filled with yellow necrotic material and in its posterior
region a haemorrhage, 3 cm in diameter, was noted. The
mass did not extend to the surface of the cortex, but did
invade and obliterate part of the left lateral ventricle.
Small multiple haemorrhages could be seen throughout
sections of the pons and midbrain.

Microscopic sections of the leptomeninges at the base
of the brain revealed an acute inflammatory reaction with
infiltration of polymorphonuclear leukocytes, but no
granuloma or PAS positive fungi were seen. Haematoxylin
and eosin stains of sections through the brain abscess
showed focal caseation necrosis with multinucleated
giant cells and scattered neutrophilic debris (Fig. 3).
Candida in the form of yeast and mycelia were demon-
strated in these areas with the use of PAS stains (Fig. 4).

DISCUSSION

Candida is an oval, budding, yeast-like fungus
which produces a pseudomycelium in culture,
tissue, and exudates. The media employed in every
typical bacteriological laboratory are adequate for
the recovery of Candida from clinical specimens,
but the organism grows most readily on Sabouraud
agar. Candida is gram-positive and is readily
demonstrated by Grocott’s methenamine silver
technique and the modified periodic acid-Schiff
method. There are seven species included in the
genus Candida, but the most common cause of
infection in man is Candida albicans. This organism
may be differentiated from the other species by
fermentation of specific chlamydospores.

CLINICAL FEATURES Candida albicans rarely invades
the central nervous system. Our review of the
literature has revealed 42 cases of cerebral candidi-
asis (see bibliography) since Heller’s first case in
1895. Fifteen of these patients either had abscess or granulomatous involvement of the brain, and 27 had meningitis without extension of the infection to the adjacent parenchyma. Thirty-five patients had one or more antecedent conditions which increased their susceptibility to fungal infections, such as antibiotic therapy, adrenocortical steroid therapy, or severe debilitating illness. In seven patients, however, no demonstrable predisposing factor could be found to account for the central nervous system candidal infection (Miale, 1943; Zimmerman, Frutchey, and Gibbes, 1947; Craig and Gates, 1949; Parrillo, 1950; Levi and Rezza, 1950; Janke, 1957; Vorreith, Bares, Benes, and Vančufík, 1961).

In the entire group of 42, there was a greater than 2 to 1 predominance of men. The age distribution showed one particularly interesting feature. Twelve patients were infants less than 1 month of age. Other authors (Seelig, 1966; Lederer and Todd, 1949) also reported the increased incidence of systemic candidiasis in the newborn infant. In most instances the source of the infection is from the birth canal, and the disease is felt to stem from the fact that newborn infants have immature immune mechanisms. In the remaining 30 patients there were eight in the first decade, three in the second, seven in the third, four in the fourth, two in the fifth, four in the sixth, and two in the seventh decade. The oldest patient was 68 years old.

The cerebrospinal fluid findings are similar to those of pyogenic bacterial meningitis. The cell count ranged from 0 to 22,560 cu. mm (Nalenz and Boese, 1951), with a preponderance of neutrophils. The spinal fluid sugar may be low or normal. The protein is usually elevated and may reach as high as 940 mg/100 ml. (Ingomar and Terslev, 1964). The spinal fluid cultures were positive for Candida albicans in nearly all the cases of meningitis. In contrast, identification of the fungus in the spinal fluid was more difficult in those patients who had brain abscess without involvement of the meninges. Therefore, the only definitive diagnostic procedure in patients with abscess or granuloma was surgical biopsy. In the four cases (including the present patient) in whom brain biopsy was performed, either by craniotomy or through trephine site, a specimen was obtained and the organism was identified as Candida albicans (Craig and Gates, 1949; Luyendijk, Welman, and Cormane, 1959; Vorreith et al., 1961).

The prognosis in cerebral candidiasis differs depending upon the nature and the site of the infection. DeVita et al. (1966) stated that the survival rate in patients with meningitis before the use of amphotericin B was 68%, and 83% after the advent of this drug. In our review of the literature, 18 of 27 patients with meningitis survived. In contrast, only one of 16 patients (including the present patient) with brain abscess or granuloma lived more than four months after the diagnosis was made (Luyendijk et al., 1959). There are a number of reasons for the poor prognosis in patients with cerebral involvement. As mentioned above, the cerebrospinal fluid cultures are frequently negative, the symptoms and signs of brain abscess are often vague, and there may be little extracranial fungal involvement to provide a useful clue for the diagnosis. Therefore, most cases of cerebral candidiasis are unsuspected during life or are diagnosed during the terminal stages of the associated illness.

Detailed neurological descriptions have been scarce. As suggested by the pathology, signs and symptoms referable to the cerebral cortex or cerebellum may dominate the clinical picture. In our patient, aphasia, hemiparesis, focal seizure, and papilloedema suggested the presence of an intracranial mass. Headache, photophobia, nuchal
rigidity, and delirium may dominate the symptoms
and signs in patients with meningitis.

PATHOLOGY AND PATHOGENESIS The kidney is the
organ most commonly involved in systemic candidiasis and death is usually secondary to kidney
failure (Louria, Stiff, and Bennett, 1962). Next
affected are the heart, lung, gastrointestinal tract,
spleen, and brain in that order (Louria et al., 1962).
Candida usually reaches the brain by the haemato-
rogenous route and its usual portal of entry into the
circulation is through the gastrointestinal tract
(Seelig, 1966), although in some cases it may come
from the respiratory system or heart (Geiger,
Wenner, Axilrod, and Durlacher, 1946). The means
by which spores gain access to the circulation
depends upon underlying conditions. According to
Seelig (1966), surfaces in contact with proliferating
organisms are more likely to be penetrated by the
fungus when their integrity is compromised. Thus
alterations in the mucous membrane surface by
inflammation, surgical trauma, local irritation from
antibiotics or Candida toxin, facilitate the pene-
tration of the fungus into the blood stream.

Microscopically, the organism provokes inflam-
mation of the affected cerebral or meningeal blood
vessels. These vessels subsequently become con-
gested and thrombosis may occur with infarction of
surrounding tissue. At the site of cerebral infarction,
necrosis, haemorrhage, and infiltration with micro-
glia and macrophages may occur along with pro-
liferation of astrocytes. Fungi can often be seen
within the infarcted area. Later, abscess or granu-
loma formation occur, although frequently these
lesions are small and often noted only on micro-
scopic examination. Multinucleated giant cells may
be present in the granulomas.

Exactly how the fungi destroy tissue or cells is
unknown, but there is evidence that the organism
may release a toxin. The exact nature of this toxic
substance has not been defined chemically or im-
umunologically. Further information about this sub-
stance can be found in a review by Friedman (1965).

TREATMENT Favourable results have been reported
after therapy with iodides (Bogen and Kessel, 1937;
Zimmerman et al., 1947; Rezza, 1950; Emdin and
Finlayson, 1954), sulphonamides (Fine, Franklin,
and Lieberthal, 1955), streptomycin (Levi and
Rezza, 1950; Nalenz and Boese, 1951; Carron and
Chavanis, 1954), propylparaben (Gessler and Laux,
1957; Janke, 1957), and nystatin (Debre, Lelong,
Mozziconacci, and Robineau, 1957; Luyendijk,
Welman, and Cormane, 1959). However, ampho-
tericin B is now the drug of choice in this dis-
ease (DeVita, Utz, Williams, and Carbone, 1966).

This drug is a polyene antibiotic which acts by
interfering with the function of the cytoplasmic
membrane of fungal cells. The current theory is that
the antibiotic binds with certain sterols in the
cellular membrane causing leakage of cytoplasmic
contents and impairment of fungal cell metabolism
(Utz, 1964). The drug is fungistatic and a total
intravenous dose of approximately 2 to 3 g is neces-
sary for therapeutic benefit.

The patient reported in this paper received 30 to
50 mg intravenous amphotericin B every other day
to a total of 430 mg. However, despite this therapy,
her neurological status worsened while her blood
urea nitrogen rose to 36 mg/100 ml. Consequently
an Ommaya reservoir was inserted into the right
lateral ventricle of the brain through which ampho-
tericin could be injected. The decision to insert the
reservoir was based on the evidence that only small
amounts of the drug cross the blood cerebrospinal
fluid barrier (Louria, 1958). It was also felt that the
reservoir permitted more prolonged and higher
peaks of intracerebral amphotericin than would
have been possible with the lumbar or intravenous
route alone. The recommended intraventricular
doze of amphotericin is 0.3 to 1.0 mg daily or every
other day depending upon patient tolerance. An
initial intraventricular dose of 1.0 mg was adminis-
tered to our patient.

There seemed to be a causal relationship between
the intraventricular injection and the patient's
subsequent worsening neurological status. Micro-
scopic examination of the meninges revealed an
acute meningitis but no evidence of granuloma or
PAS positive staining fungi. This raises the pos-
sibility of a meningitis caused by the amphotericin
itself. Chemical meningitis as a result of lumbar
intrathecal injections of amphotericin rarely occurs
(Spickard, Butler, Andriole, and Utz, 1963), but the
incidence of meningitis after intraventricular in-
jections has never been recorded. Perhaps the dosage
of the initial injection is an important contributing
factor in the formation of the acute meningeal
inflammation. It may well be that 1 mg ampho-
tericin was an excessive initial intraventricular dose
for our patient.

AETIOLOGY Debilitating disease, antibiotic therapy,
and adrenocortical hormones acting either alone or in
combination seem to predispose to disseminated
candidiasis. There is at present no explanation for
this predisposition, but it seems probable that the
infection is related in some way to suppression of
normal immunity mechanisms.

Occasionally central nervous system candidiasis
occurs in patients in whom no predisposing medi-
cation or illness can be found. The aetiology of the
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infection in these individuals is not clear, but it may be related in part to the virulence of the infecting strain of Candida albicans (Louria et al., 1962). The mechanism of tissue localization in these individuals is also uncertain, but there is some experimental evidence that suggests that certain strains and species of Candida have a predilection for brain tissue. Smith and Sano (1933) studied a strain of Candida albicans acquired from the brain of one patient and reported that it was neurotropic when injected into rabbits. Also Louria et al. (1962) showed that certain species of Candida regularly produced central nervous system infection in mice after intravenous injection. However, despite the fact that certain strains and species of Candida seem neurotropic in experimental animals, no conclusions can be drawn concerning the possibility that the course and tissue localization of human candidiasis is related to characteristics of the invading strain of Candida organisms (Louria et al., 1962).

It may also be argued that apparently healthy individuals who develop such dissemination actually suffer from a specific immunological or enzymatic defect which does not ordinarily manifest itself as an impairment in general health. Recently, Lehrer and Cline (1969) discovered that the neutrophils and monocytes of an otherwise healthy patient afflicted with disseminated Candida albicans infection lacked detectable levels of the lysosomal enzyme myeloperoxidase. They concluded that this enzyme was specifically necessary for the killing of Candida organisms by human white blood cells after phagocytosis. However, disseminated candidiasis due to a specific susceptibility engendered by the lack of leukocyte myeloperoxidase is unlikely in our patient, for she had a normal amount of this enzyme in her neutrophils. There is the possibility that our patient lacked another, as yet undelineated, neutrophilic enzyme that is specifically necessary for candidicidal activity.

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