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Prostatic sequestration of *Cryptococcus neoformans* in immunocompromised persons treated for cryptococcal meningoencephalitis

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Summary. We report a case of a patient with acquired immune deficiency syndrome who was successfully treated for cryptococcal meningoencephalitis with amphotericin B and 5-flucytosine. He died from other sequelae of acquired immune deficiency syndrome two years later. An autopsy revealed prominent cryptococcal prostatitis. Cryptococci were neither found in the central nervous system nor in other anatomic sites.

The autopsy files yielded seven other cases of men with a history of cryptococcal meningoencephalitis. The possibility that the prostate sequesters *Cryptococcus neoformans* thereby contributing to systemic relapse is explored. To qualify as a sequestration, cyptococci must be cultured from the prostate, or from a midstream voided specimen after prostatic massage, and the prostate must be the only focus of infection.

Key words: Acquired immunodeficiency syndrome, Cryptococcosis, Encephalitis, Prostate, Autopsy

Introduction

Cryptococcus neoformans is found up to 11% of AIDS cases (Eng et al., 1986; Zuger et al., 1986; Longengo et al., 1993). The disease usually presents as meningitis and encephalitis with fever and headache (Kovacs et al., 1985; Zuger et al., 1986). Disseminated disease is more common in AIDS patients than in other patients with *C. neoformans* (Eng et al., 1986). The mainstay of treatment has been amphotericin B with or without 5-flucytosine (5-FC) (Eng et al., 1986; Saag et al., 1992). Kovaks et al. (1985) reported on 24 AIDS patients with cryptococcosis who were treated with amphotericin B, with or without 5-FC; 4 showed a sustained response to therapy, 6 relapsed after initial negative cultures, and 14 were treatment failures. The use of amphotericin B has been hampered by its undesirable side effects including renal dysfunction, fever, and chills, and the need for intravenous administration. Triazole antimicrobial agents, such as fluconazole, and intraconazole, are active against *C. neoformans* after oral administration. Recent investigations have evaluated the drugs in *C. neoformans* prophylaxis (Loveless et al., 1993), as alternatives to amphotericin B (Saag et al., 1992; Milefchik et al., 1993; Taelman et al., 1993a), and in longterm maintenance or suppressive therapy following a course of amphotericin B (Powderly et al., 1992; Taelman et al., 1993b). They are better tolerated than amphotericin B (Saag et al., 1992; Taelman et al., 1993a). Early reports of a liposomal formulation of the latter suggest that it is significantly less toxic than amphotericin B (Coker et al., 1993; Roberto et al., 1993).

It has been hypothesized that *C. neoformans* is sequestered in the prostate (Larsen et al., 1989; Staib et al., 1990) from where it may cause relapse of systemic disease. We found cryptococcal prostatitis at postmortem examination in an AIDS patient who had been successfully treated for cryptococcal meningoencephalitis two years prior to death. The patient was a participant of the Multicenter AIDS Cohort Study (MACS), a prospective longitudinal study of the natural history of HIV infection (Kaslow et al., 1987a,b). Clinical information and prospectively archieved urine samples permitted investigation into whether or not the prostatic focus of cryptococcosis represented a sequestration.

To determine the prevalence of prostatic cryptococcosis in autopsies at Presbyterian University Hospital, Pittsburgh, PA, we reviewed the hospital's autopsy logs for men with antemortem or postmortem diagnosis of cryptococcal meningoencephalitis.

Materials and methods

The index case was a participant of the Multicenter

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AIDS Cohort Study (MACS), a longitudinal study of the natural history of HIV infection in homosexual and bisexual men. The study was begun in 1984. The men are seen semiannually for physical examination, and collection of epidemiologic information and specimens (Kaslow et al., 1987a,b). Urine was collected from 1984 to 1987 and stored at -70 °C.

The patient had been treated for cyptococcal meningoencephalitis in 1988 and died two years later from unrelated causes. An autopsy was performed. Fourteen urine specimens were available for study. Autopsy prostatic tissue, and antemortem urine samples were cultured for fungi by standard methods on Sabouraud dextrose agar (SDA), Sabhi medium, SDA with chloramphenicol and gentamicin, brain heart infusion agar (BHI) with blood, and mycobiotic agar at 30 °C for 2 weeks. Mycobiotic agar is manufactured by Difco Laboratories (Detroit, MI). The other media are manufactured by Remel (Lenexa, Kansas).

Reviews of Logs of Postmortem Examinations

Autopsies between 1970 and 1990, of men with antemortem or postmortem diagnosis of cryptococcal meningoencephalitis were retrieved from the neuropathology and autopsy logs at Presbyterian University Hospital, Pittsburgh, PA and reviewed.

Results

Report of a case

This 39 year-old homosexual man was HIV seropositive in 1984. Beginning in 1986, he had many bouts of *Pneumocystis carinii*, pneumococcus, klebsiella, legionella, and aspergillus pneumonia. Mucocutaneous *Herpes simplex*, cryptococcal meningoencephalitis, cryptosporidial diarrhea, gonorrhea, syphilis, adrenal cortical insufficiency, and Kaposi's sarcoma were also diagnosed.

In December of 1988 the patient presented to the hospital with headache. Cerebrospinal fluid (CSF) cryptococcal antigen titer was 1:16. CSF culture yielded *C. neoformans*. The patient was administered intravenous amphotericin B (total dose 1 gram), and 2.25 g 5-FC orally every six hours for three weeks. At the completion of the course of therapy, CSF culture was negative for fungi. The cryptococcal antigen titer was positive at 1:1. The patient was discharged on 250 mg of 5-FC every other day.

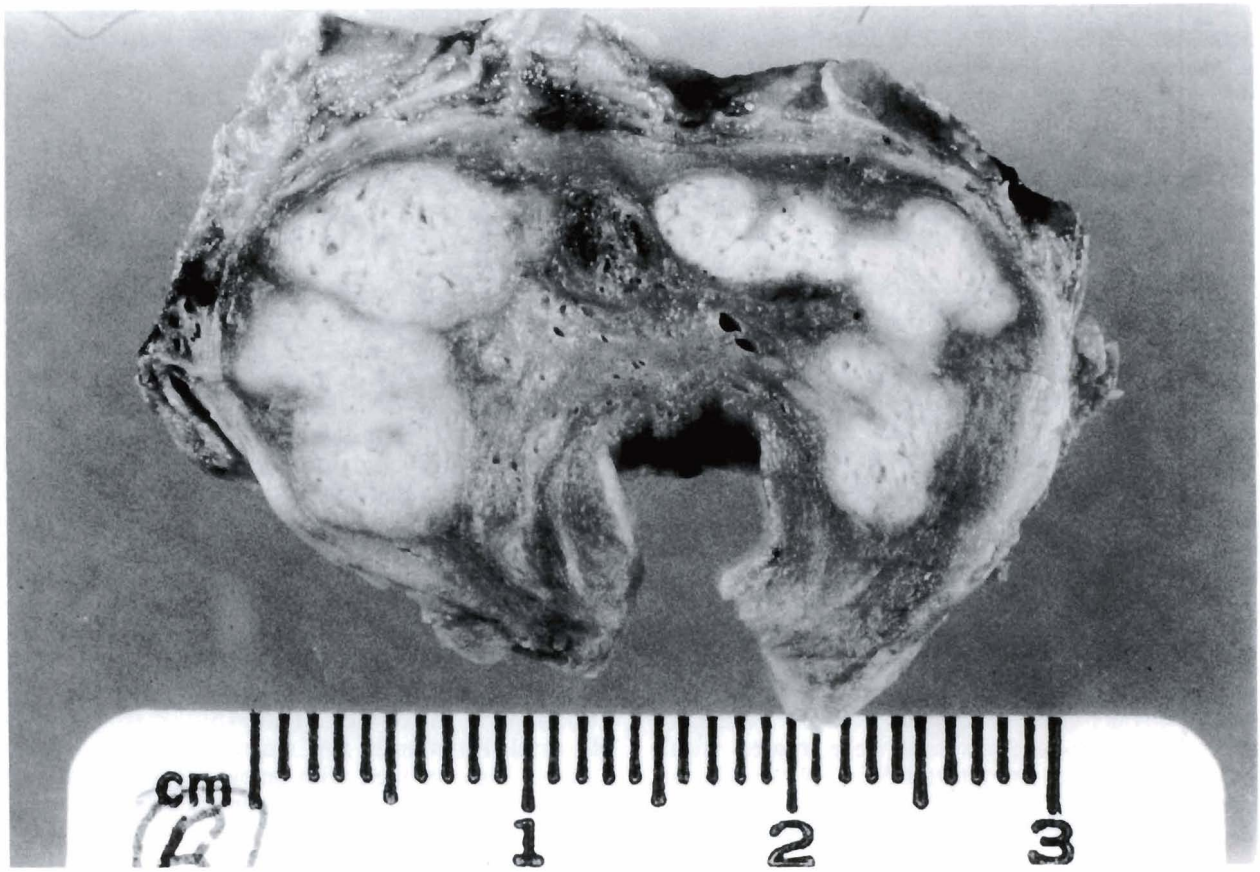

Fig. 1. Cross section of the prostate shows multiple focally confluent pale nodules which rim in the urethra (case 1, Table 1).

In November, 1990, he had a bout of hemorrhagic bronchopneumonia and died. At autopsy, the prostate gland was of normal color and consistency. Upon sectioning, the parenchyma showed a bean-shaped cream-yellow, 3 by 0.7 cm focus bilaterally (Fig. 1). The lesion was 0.2 cm from the urethra, focally. Microscopic examination revealed several infarcts with scattered calcific material. There were scant normal glandular elements. At high power, many imperfectly round, occasionally cup-shaped, variably sized, 6 to 12 micrometer, translucent organisms were seen. Mucicarmine and Grocott methenamine silver (GMS) showed narrow base budding yeasts (Fig. 2) consistent with *C. neoformans*. There were no inflammatory cells.

Other findings at autopsy included candidal abscesses in the left kidney, and aspergillus and candidal abscesses in the skin. Cachexia, cytomegalovirus adrenalitis, pneumonitis, and encephalitis, and multiple lesions of *Molluscum contagiosum* were also noted.

Antemortem urine samples and autopsy log review

The urine samples were negative for *C. neoformans*. *Candida albicans* was cultured from a 1986 urine sample. Prostatic tissue collected at autopsy was negative for fungi. Review of the autopsy logs yielded eight cases of cryptococcal meningoencephalitis (Table 1) including the index case (case 1). Cryptococcosis of the prostate and kidney were found in a 19 year-old with acute lymphocytic leukemia (ALL) (case 2, Table 1, Fig. 3).

Case 6 (Table 1) had a fibrosed focus in the prostate

Table 1. Cryptococcal meningitis at Presbyterian University Hospital, Pittsburgh, PA. Males 1970-1990.

CASE	AGE	RACE	UNDERLYING DISEASE	YEAR OF DEATH	TIME TO DEATH AFTER DIAGNOSIS OF CRYPTOCOCOSIS	TREATMENT	COURSE OF CRYPTOCOCCAL MENINGITIS	CRYPTOCOCCAL ANTIBODY TITER	CRYPTOCOCCAL MENINGITIS AT AUTOPSY	GENITOURINARY TRACT FINDINGS
1	39	W	AIDS	1990	2 years	Amphotericin B 5-Flucytosine	Resolved	1:16	no	Cryptococcosis, Prostate Testicular atrophy
2	19	W	ALL	1973	1 month	Amphotericin B	Persistent?		yes	Cryptococcosis, Prostate Cryptococcosis, Kidney
3	57	W	AIDS	1986	9 months	Amphotericin 5-Flucytosine	Relapsing	1:256	yes	Prostate not sampled Testicular atrophy Nephrocalcinosis
4	42	W	AIDS/Hemophilia A	1985	8 months	Amphotericin B	Persistent?		yes	Testicular atrophy Nephrocalcinosis
5	50	W	Adenocarcinoma Kidney	1985	Postmortem	Not applicable	Terminal?		yes	Prostate not sampled Aspermia Adenocarcinoma, Kidney
6	67	W	Diabetes Mellitus Rheumatoid arthritis	1975	Terminal	Not applicable	Terminal?		yes	Nodular hyperplasia prostate
7	72	W	CLL	1979	Terminal	Amphotericin B	Persistent		yes	Nodular hyperplasia, prostate
8	49	W	Cirrhosis	1987	2 years	Amphotericin B	Persistent	*	yes	Testicular Atrophy S/P Left nephrectomy

*: not availabe; AIDS: acquired immunodeficiency syndrome; ALL: acute lymphocytic leukemia; CLL: chronic lymphocytic leukemia; W: white.

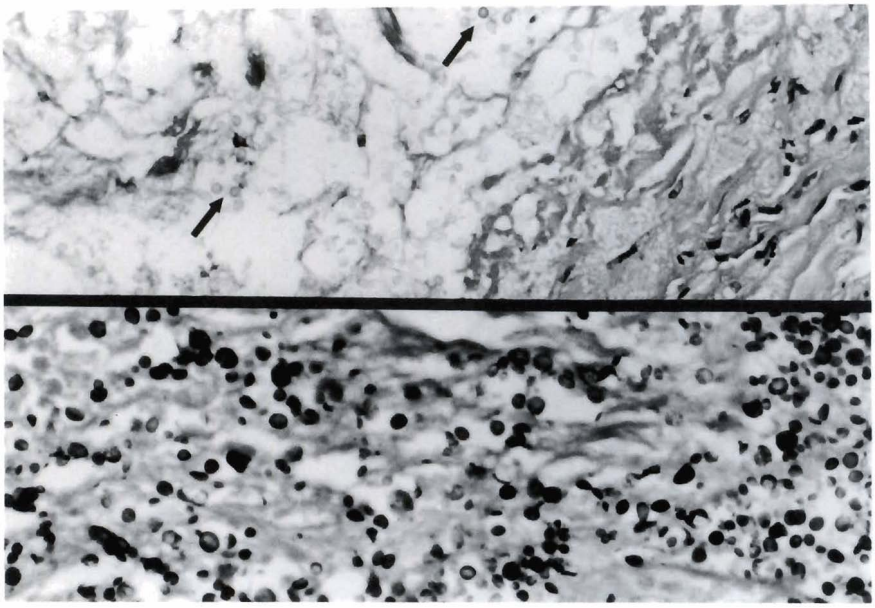

Fig. 2. (Above) High power view of the prostate with gelatinous background with scattered organisms (arrows) and rare inflammatory cells. H & E stain. Case 1, Table I). (Below) Imperfectly round organisms of varied size. GMS, Case 1, Table 1. x 400

which suggested a prior infarction (and possibly infection). Histologic sections of the prostate in the remaining cases revealed benign nodular hyperplasia, and scattered small calcification. Calcific deposits were noted in kidneys of two AIDS patients with active meningoencephalitis.

Discussion

Persistence of *C. neoformans* in the urine has been described after therapy with fluconazole (Bailly et al., 1991; Bozzette et al., 1991), itraconazole (Staib et al., 1990), and amphotericin B (Larsen et al., 1989). Pyelonephritis like prostatitis not uncommonly persists when *C. neoformans* is extirpated from the brain and meninges by standard therapy (Hellman et al., 1981). The absence of organisms in the urine before and their presence after prostatic massage is indicative of prostatic rather than renal cryptococcosis. Larsen et al. (1989) showed cryptococcal organisms after prostatic massage in 4 of 9 patients with post-treatment funguria.

Genito-urinary eradication of *C. neoformas* is not always assessed in published reports of cryptococcal meningoencephalitis. Saag et al. (1992) required cultures to be negative to consider treatment successful; urinary cultures were exempt from this requirement (an acknowledgement of the difficulty in eradicating the organism). Other reports do not include data on urine culture (Eng et al., 1986; Zuger et al., 1986; Bolignano et al., 1991). Patients who do not clear the urine of organisms following therapy are clinically indistinguishable from those who do (Larsen et al., 1989).

As noted, culture positive urine or prostatic tissue is the *sina qua non* of genitourinary cryptococcosis. Histological demonstration of the organisms on the other hand can be misleading; this does not demonstrate that the organism are viable and a potential source of relapse. Huynh and Reyes (1982) reported a case of recurrent dysuria and hematuria which was followed up for eight years; histological examination showed cryptococcal prostatitis on several occasions but the organism was never grown. Prostatic tissue from the case presented here (case 1, Table 1) did not yielded cryptococci on culture.

Evidence for sequestration

A review of cryptococcal prostatitis in 1981 yielded 15 cases (Hinchey and Someren, 1981); the underlying diagnoses were diabetes mellitus (2), rheumatoid arthritis (2), sarcoidosis (1), and lymphohematopoietic malignancies (3). Six patients did not have identifiable predisposing conditions. An additional case was described a month later in a patient with chronic active hepatitis and a history of tuberculosis (Braman, 1981). A recent report described cryptococcal prostatitis following orthotopic cardiac transplantation (Case Records of the Massachusetts General Hospital, 1994). The AIDS era ushered in a markedly increased number of immunocompromised persons, and undoubtedly cryptococcal infections and complications thereof (Kovacs et al., 1985). The first report of prostatic cryptococcosis in AIDS appeared in 1986 (Lief and Sarfarazi, 1986).

The existence of a sequestration phenomenon is anecdotal. Staib et al. (1990) described a case of persistent culture-proven prostatic cryptococcosis with declining antigen titers and hypothesized that antifungal agents do not have the requisite «pharmacokinetics under defined pathological-anatomical conditions» to eradicate the infection from the prostate. This perpetuated a previously espoused explanation (Larsen et al., 1989) for the frequent relapses of treated

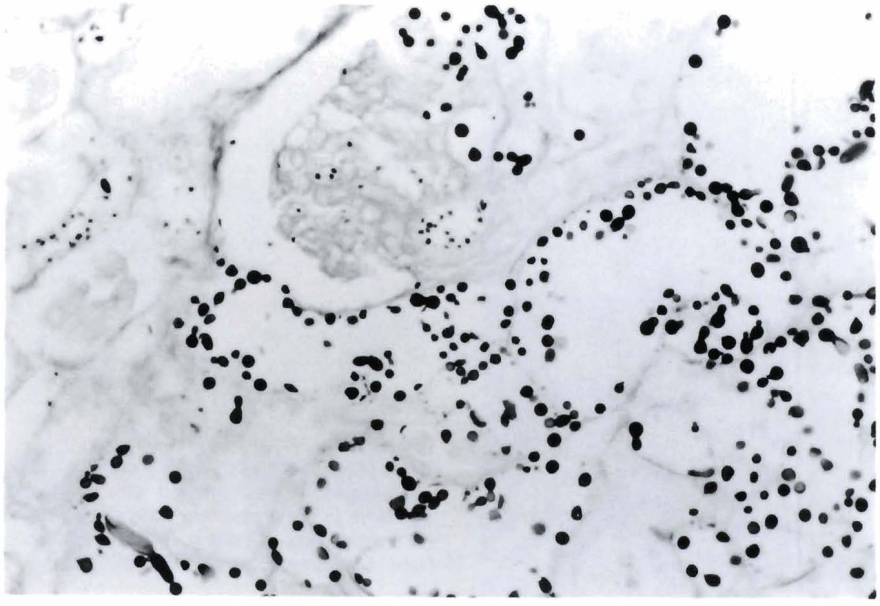

Fig. 3. GMS stained section of the kidney demonstrates organisms in a glomerulus and tubules. Case 2, Table 1. x 250

cryptococcal infection. Case 1 (Table 1) appears to have been adequately treated for cryptococcal meningoencephalitis, and did not have a viable focus from which there could be relapse, in spite of the florid prostatic cryptococcosis at autopsy.

It is clear that to qualify as a sequestered prostatic focus from which relapse is possible, it is necessary to demonstrate *C. neoformans* from culture of the prostate or from prostatic secretions (including urine following prostatic massage), and the prostate must represent the only focus of residual infection. Of the five other cases of cryptococcal meningoencephalitis which could be evaluated for prostatic cryptococcosis (the prostate was not sampled in cases 3 and 5, Table 1), only case 2 with terminal disseminated cryptococcosis had incontrovertible evidence of prostatic involvement.

Though incomplete, the emerging picture suggests that the presence or absence of a genito-urinary focus of infection may be one of many factors that determines the outcome of cryptococcal meningoencephalitis. Efforts should be directed at prophylaxis of persons who are prone to the disease and to relapse.

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