Meningitis Caused by *Pseudallescheria boydii*

Teng-Yeow Tan, MD; Chia-Wei Liou, MD; Ling-Chang Kung[1], MD

We present a 43-year-old immunocompetent man who developed meningitis caused by *Pseudallescheria boydii*. The patient had no history of near drowning, trauma, steroid administration, operations or any other underlying systemic disease. He presented with intermittent fever associated with headache, bilateral eye pain, and vomiting. Progressive hydrocephalus was noted during the course of the disease. Cerebrospinal fluid (CSF) from the ventricular system allowed culture of the organism. Although the disease was diagnosed antemortemly, the patient died after antifungal treatment. This case is reported because of the unusual pathogen, unresponsiveness to amphotericin B combined with 5-fluocytocin, and immunocompetence of the patient without any predisposing factors. *(Chang Gung Med J 2004;27:228-32)*

Key words: meningitis, *Pseudallescheria boydii*, hydrocephalus, diagnosis, therapies.

Pseudallescheria boydii (P. boydii) is a dimorphic fungus that has been isolated from soil, decaying vegetation, poultry and cattle manure, polluted streams, and coastal water. *Allescheria boydii* and *Petriellidium boydii* (the sexual form) and *Monosporium ampiospermum and Scedosporium ampiospermum* (the asexual form) have been previously used as species names.[1] The fungus produces little immunological reaction, and when infected can proliferate, destroy soft tissue, and produce granulomas, sinus tracts, and osseous rarefaction.[2] It is the most frequent etiologic agent of mycetoma in temperate regions of the world[3] and has been reported to cause various focal organ infections and disseminated infections.[4] The patients are usually immunocompromised, debilitated, or have history of trauma. In addition to causing Madura foot, it is frequently found within pulmonary cavities, but the central nervous system involvement presenting as persistent neutrophilic meningitis is extremely rare.[5] We present a healthy, immunocompetent patient who developed meningitis caused by *P. boydii*.

CASE REPORT

A 43-year-old man presented with intermittent fever for 3 months which was associated with headache, bilateral eye pain, and vomiting. Detailed studies including chest X-ray, urine analysis, abdominal ultrasound, bone scan and a Gallium scan all showed negative results. Laboratory examination results, including a complete blood count, renal function, liver function, and electrolytes, were normal. Human immunodeficiency virus test and bacteria/fungus culture results were negative. Meningeal irritation signs and bilateral chronic papilledema were found during neurological examinations. An initial brain computed tomogram (CT) with contrast enhancement showed negative findings. Serial cerebrospinal fluid (CSF) analysis revealed persist neutrophilia, but negative cultural results for bacteria and fungus (Table 1). The patient was treated for bacterial meningitis with empirical antibiotics. Sequential follow-up brain CT scans revealed progressive hydrocephalus and the enhanced brain CT

From the Department of Neurology, Chang Gung Memorial Hospital, Kaoshiung; [1]Department of Neurology, Ping-Tung Christian Hospital, Ping-Tung, Taiwan.
Received: Mar. 14, 2003; Accepted: Jul. 4, 2003
Address for reprints: Dr. Chia-Wei Liou, First Department of Neurology, Chang Gung Memorial Hospital. 123, Dabi Road, Niaosung Shiang, Kaohsiung, Taiwan 833, R.O.C. Tel.: 886-7-7317123 ext. 2283; Fax: 886-7-7318762; E-mail: cwliou@ms22.hinet.net

Table 1. Serial CSF Findings

Days after onset of symptoms	3†	10	24	30	41	56	63‡	67
WBC	260	1082	860	510	88	258	1330	99
lymphocytes (%)	56	6	24	18	12	6	4	4
Monocytes (%)	2	12	6	6	1	13	7	4
Neutrophils (%)	42	82	70	76	87	81	89	92
Glu (c/s) (mg/dl)	29/124	29/109	26/125	43/130	47/165	59/148	59/136	62/129
Protein (mg/dl)	181	150	99	180	36	65	109	53
Lactate (mg/dl)	35	52	45	45	44	34	50	79
Culture								
bacteria	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
fungus	(-)	(-)	(-)	(-)	(-)	(-)	P boydii*	P boydii*
T.B	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Cryptococcus Ag	(-)							

C: CSF, S: serum; T.B: tubeculous bacilli.

* CSF culture from shunt.

† antibiotics given

‡ amphotericin B combined with 5-fluocytocin therapies given.

showed no abscess formation. A shunt was inserted to relieve hydrocephalus. The CSF obtained from the shunt (day 63 and 67) gave positive fungal culture of *P. boydii*. The patient died a month after proven diagnosis despite the use of amphotericin B and 5-fluocytocin therapy.

DISCUSSION

CNS infection caused by *P. boydii* was first reported in 1953.[6] Symptoms and signs are nonspecific but neurological deficits correlate well with the location involved in CNS. Although one third of the patients with CNS infection caused by *P. boydii* have clinical or radiological involvement other than CNS, no other site of infection was found in our case. Apparent risk factors of CNS infection included near-drowning in polluted waters, granulocytopenia, T-cell immunosupression, and trauma. Medical immunosuppression and near-drowning episodes were the most frequent (60%) risk factor for CNS pseudallescheriasis, about 15% of the cases revealed no identified risk factors.[7] No apparent risk factor was found in our case. Walker et al.[8] suggested that *P. boydii* enters the body as an airborne organism through the pulmonary system and hematogenously to CNS. However, CNS infection via direct inoculation after trauma or surgery, by extension of a focus of infection in the vicinity of the CNS, by association with ventricular CSF drainage devices or after rachianesthesia procedures may also occur. Although direct inoculation after surgery and lumbar puncture were the possible routes of the fungus to the CNS in our patient and medical immunosuppression causing secondary infection in the late course of treatment in this case should be considered, the persistent increase of neutrophils in the serial CSF analysis suggested that the *P. boydii* was the primary infectious pathogen in the beginning of the disease.

Persistent neutrophilia in the serial CSF analysis in our case showed the unusual finding of CNS infection caused by *P. boydii*. From the review of Nesky et al.,[7] brain abscess comprised approximately 80% of CNS pseudallescheriasis whereas 28% of the cases presented as meningitis. A review by Kershaw et al. showed that only half of the reported cases revealed a predominance of neutrophils in the CSF and CSF obtained from ventricular drainage or shunt yields higher positive culture rates.[9] Physicians should strongly suspect the possibility of actinomycosis, norcardiosis, aspergillosis, zygomycosis or pseudallescheriasis in patients with persistence of neutrophils in the CSF.[10] Under normal circumstances, neutrophil chemotactic factors are derived from the interaction of an organism and its products with a variety of the host defense systems especially complement pathogens[11] and intracellular pathogens. They elicit initial neutrophilic host

responses which would be supplanted by a mononuclear response in cases of persistent disease. Conversion to a mononuclear cell response did not occur in our patient with meningitis. The mechanism by which the generation of the neutrophil chemotactic factors continued in this patient is not clear but Chinn and Diamond suggested that the neutrophil response was due to the presence of mycelia and hyphae.[12]

The diagnosis of *P. boydii* infection depends on visualization of the septate hyphae or culture and staining of biopsied tissue with fluorescent antibodies. Prompt antemortem diagnosis is therefore not easy due to the rarity of this infection and the lack of specific and sensitive serological and culture tests. It is also complicated by the cross-reactivity to *P. boydii* antigens in the Cryptococcus capsular antigen latex test.[13] Morphologically, dilated, swollen hyphal segments and the pattern of hyphal branching are helpful in differentiating it from similar fungi.[14] Newly developed fluorescent-antibody reagents using adsorbed reagents to detect and identify *P. boydii* provide a rapid, reliable method for histological diagnosis of pseudallescheriasis.[15] Application of a staining procedure with optical brighteners on smears of enriched CSF cells or brain biopsy specimens can offer a crucial improvement in the identification of mycotic CNS infections during life.[16] In our case, as this fungus was cultured from CSF obtained from the shunt, this implies that the concentration of the fungus was high in the ventricle. The CSF obtained from the ventricular system may increase the positive culture rate of the pathogen and other authors have recommended the examination and culture of the ventricular or cisternal CSF in cases where lumbar CSF fails to establish a diagnosis.[17]

Although amphotericin B is the standard antifungal agent for the empirical treatment of fungal infections, *P. boydii* is often resistant to amphotericin B. Most isolates of *P. boydii* appear to be sensitive to miconazole, ketoconazole and itraconazole. A combination of miconazole and ketoconazole has showed clinical stabilization and gives survival to patients, suggesting a possible role for dual drug therapy.[18] Miconazole given either intrathecal or via a shunt has been reported to be successful in treatment of infections due to *P. boydii*,[19] and voriconazole, a second-generation azole antifungal agent, has been approved for the treatment of infections due to *P. boydii* in the United States.[20]

CNS infection caused by *P. boydii* is usually fatal but among patients with solitary or contiguous abscesses, the prognosis is better.[21] Prompt diagnosis, appropriate treatment, and surgical intervention may improve the prognosis but the major problem is the difficulty in culturing the organism antemortemly which creates a delay in appropriate therapy. Clinicians should maintain a high index of clinical suspicion with regard to the patients with persistent neutrophilic meningitis and clinical deterioration. *P. boydii* must be included as an etiologic agent of chronic meningitis even in immunocompetent hosts.

REFERENCES

1. Rippon JW. Medical mycology: The pathogenic fungi and pathogenic actinomycetes. 2nd edition. Philadelphia WB. Saunders. 1982;595-614.
2. Selby R. Pachymeningitis secondary to *Allescheria boydii*. Neurosurg 1972;36:225-7.
3. Welsh O. Mycetoma. Current concepts in treatment. Int J Dermatol 1991;30:387-98.
4. Travis LB, Roberts GD, Wilson WR. Clinical significance of *Pseudallescheria boydii*: a review of 10 years' experience. Mayo Clin Proc 1985;60:531-7.
5. Peacock JE Jr. Persistent neutrophilic meningitis. Infect Dis Clin North Am. 1990;4:747-67.
6. Aronson SM, Benham R, Wolf A. Maduromycosis of the central nervous system. J Neuropathol Exp Neurol 1953; 12:158-68.
7. Nesky MA, McDougal EC, Peacock JE Jr. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. Clin Infect Dis 2000;31:673-7.
8. Walker DH, Adamec T, Krigman M. Disseminated petriellidosis (allescheriosis). Arch Pathol Lab Med 1978;102:158-60.
9. Kershaw P, Freeman R, Templeton D, DeGirolami PC, DeGirolami U, Tarsy D, Hoffmann S, Eliopoulos G, Karchmer AW. *Pseudallescheria boydii* infection of the central nervous system. Arch Neurol 1990;47:468-72.
10. Hooper DC, Pruitt AA, Rubin RH. Central nervous system infection in the chronically immunosuppressed. Medicine 1982; 61:166-88.
11. Wilkinson PC. Leukocyte locomotion and chemotaxis: Effects of bacteria and viruses. Rev Infect Dis 1980; 2: 293-318.
12. Chinn R, Diamond RD. Chemotactic factors for human neutrophils generated by *Rhizopus oryzae*. Clin Res 1982;30:363A.

13. Wilichowski E, Christen HJ, Schiffmann H, Schulz-Schaeffer W, Behrens-Baumann W. Fatal *Pseudallescheria boydii* panencephalitis in a child after near-drowning. Pediatr Infect Dis J 1996;15:365-70.
14. Schwartz DA, Amenta PS, Finkeletein SD. Cerebral *Pseudallescheria boydii* infection: unique occurrence of fungus ball formation in the brain. Clin Neurol Neurosurg 1989;91:79-84.
15. Jackson JA, Kaplan K, Kautmann L, Standard P. Development of fluorescent-antibody reagents for demonstration of *Pseudallescheria boydii* in tissues. J Clin Microbiol 1983;18:668-73.
16. Ruchel R, Margraf S. Rapid microscopical diagnosis of deep-seated mycoses following maceration of fresh specimens and staining with optical brighteners. Mycoses 1993;36:239-42.
17. Edwards VE, Sutherland JM, Tyrer JH. Cryptococcosis of the central nervous system. Epidemiological, clinical, and therapeutic features. J Neurol Neurosurg Psychiatry 1970;33:415-25.
18. Schiess RJ, Coscia MF, McClellan GA. *Petriellidium boydii* pachymeningitis treated with miconazole and ketonazole. Neurosurg 1984;14:220-4.
19. Walsh TW, Peter J, McGough DA, Fothergill AW, Rinaldi MR, Pizzo PA. Activities of amphotericin B and antifungal azoles alone and in combination against *Pseudallescheria boydii*. Antimicrobial Agents Chemotherapy 1995;39:1361-4.
20. Johnson LB, Kauffman CA.Voriconazole: a new triazole antifungal agent. Clin Infect Dis 2003;36:630-7.
21. Dworzack DL, Clark RB, Borkowski WJ, Smith DL, Dystra MP, Pugsley MP, Horowitz EA, Connlly TL, McKinney DL, Hostetler MK, Fitzgibbons J, Galant M. *Pseudallescheria boydii* brain abscess: Association with near-drowning and efficacy of high-dose, prolonged miconazole therapy in patients with multiple abscesses. Medicine 1989;68:218-24.

*Pseudallescheria boydii*腦膜炎

陳廷耀 劉嘉爲 孔令璋[1]

本病例爲43歲男性，因持續頭痛、發燒、雙眼疼痛而住院。追溯其過去史無特殊處，理學檢查除頸部僵硬外無其他異常。多次腦脊髓液追蹤檢查顯示持續有嗜中性白血球偏高，多次腦脊髓液培養無細菌、結核菌或眞菌生長。經抗生素治療，住院兩個月後腦部電腦斷層攝影檢查顯示有腦室積水現象，病人因而接受腦室腹腔引流手術，而自引流管獲得之腦脊髓液中，培養出*Pseudallescheria boydii*。後雖經改用Amphoteicin B合併5-fluocytocin 治療，病人仍於住院三個月後死亡。本病例之特點爲*Pseudallescheria boydii* 所引起之持續嗜中性白血球腦膜炎且無誘因可循。(長庚醫誌 2004;27:228-32)

關鍵字: 腦膜炎，*Pseudoallescheria boyii*，水腦症，診斷，治療。

長庚紀念醫院 高雄院區 神經內科一科；[1]屏東基督教醫院 神經內科
受文日期：民國92年3月14日；接受刊載：民國92年7月4日。
索取抽印本處：劉嘉爲醫師，長庚紀念醫院 神經內科一科。高雄縣833鳥松鄉大埤路123號。Tel.: (07)7317123轉2283; Fax: (07)7318762; E-mail: cwliou@ms22.hinet.net