Original article

CRYPTOCOCCAL MENINGITIS IN PATIENTS NOT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

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Abstract  A retrospective study was carried out at Maharaj Nakorn Chiang Mai Hospital from January 1997 to December 2003 to assess the clinical features, laboratory data, and clinical outcome of 12 non-HIV infected patients with cryptococcal meningitis. There were 5 men and 7 women; the mean age was 50.8 years (range, 19-77 years). Eight patients did not have any underlying disease. The most common presentations were fever and headache. Stiffness of neck was found in half of the patients. Five of eleven patients had a positive India ink test. All patients were treated with amphotericin B. Two patients died. Both of them had severely impaired consciousness at the time of admission. Chiang Mai Med Bull 2006; 45(3):119-125.

Keywords: Cryptococcal meningitis, non-HIV infected patients

Cryptococcal meningitis is the most common form of disease caused by Cryptococcus neoformans, an encapsulated yeast. There are two varieties of C. neoformans, namely variety neoformans and variety gatti. C. neoformans variety neoformans is found in aged pigeon droppings and causes disease in immunocompromised patients including AIDS patients. C. neoformans variety gatti is not associated with birds, but grows in the litter around certain species of eucalyptus trees and causes disease in immunocompetent hosts. However, cases were also reported in patients who had no underlying diseases. With the advent of the AIDS epidemic, the number of cryptococcal meningitis cases increased dramatically and there have been many case series reported worldwide. However, there is still little known about the disease in patients not infected with HIV.

This study reviewed cases of cryptococcal meningitis in patients not infected with HIV at Maharaj Nakorn Chiang Mai Hospital.
Patients and methods

We conducted a retrospective chart review of patients diagnosed as cryptococcal meningitis, who were not infected with HIV and admitted at Maharaj Nakorn Chiang Mai Hospital between January 1997 and December 2003. The diagnosis was made by isolating *Cryptococcus neoformans* from a cerebrospinal fluid (CSF) specimen. The cultures were performed at the central laboratory of Maharaj Nakorn Chiang Mai Hospital.

Information extracted from the medical records included demographic data (age, sex, occupation, and address), symptoms and signs, underlying medical conditions, results of laboratory tests including central nervous system imaging, and outcome.

Demographic data, symptoms and signs, and outcome of the patients were reported as percentage, mean, range, and standard deviation (SD), as appropriate.

Results

There were 15 patients examined during the study period, and medical records were obtained from 12 of them. There were, therefore, 5 men and 7 women, with a male to female ratio of 0.7:1. The mean age was 50.8±
Cryptococcal meningitis is common among persons aged 30-40 years. Men are more often affected than women. Conditions with impaired cellular immunity such as AIHA, SLE, and idiopathic CD4+ lymphopenia predispose the patients to this infection. In our study, the underlying diseases could be identified in 33.3% of the patients, compared to the 25% reported in other studies.

The clinical course of cryptococcal meningitis is often insidious, ranging from subacute meningitis to meningoencephalitis. In immunocompromised patients, fever and headache might not be present. Because of the low index of suspicion, the diagnosis is often delayed, resulting in poor prognosis.

The gold standard for the diagnosis is the recovery of Cryptococcus neoformans from the CSF. Other CSF findings included pleocytosis with mononuclear cell predominance. The CSF findings are similar to those in HIV-infected patients with cryptococcal meningitis. However, the latter usually showed less CSF pleocytosis. HIV-infected patients with cryptococcal meningitis have a positive India ink test more frequently at about 70%, compared to 50% in our study.

Each cryptococcal antigen test has the sensitivity and specificity of more than 90%, even in patients with a negative India ink test. In our study, the cryptococcal antigen test was carried out in 11 cases. It was negative in one patient who had SLE and showed a low titer in another who had AIHA.

Cryptococcoma, especially of the spinal cord, is a rare condition. Most of the cryptococcoma cases in immunocompetent hosts are caused by Cryptococcus neoformans.
<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
<tr>
<td>sex</td>
<td>Male</td>
<td>Female</td>
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<tr>
<td>Age (years)</td>
<td>40</td>
<td>62</td>
<td>51</td>
<td>52</td>
<td>66</td>
<td>64</td>
<td>77</td>
<td>45</td>
<td>42</td>
<td>19</td>
<td>46</td>
<td>71</td>
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<tr>
<td>Underlying diseases</td>
<td>TB</td>
<td>DM, Adrenal Insufficiency</td>
<td>Confusion</td>
<td>Headache, lung mass</td>
<td>Tetraplegia</td>
<td>Headache, ataxia</td>
<td>Headache, confusion</td>
<td>Headache, ataxia</td>
<td>Headache, confusion</td>
<td>Headache, confusion</td>
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<tr>
<td>Presentation</td>
<td>Headache, confusion</td>
<td>Confusion</td>
<td>Headache, lung mass</td>
<td>Headache, ataxia</td>
<td>Tetraplegia</td>
<td>Headache, ataxia</td>
<td>Headache, confusion</td>
<td>Headache, ataxia</td>
<td>Headache, confusion</td>
<td>Headache, confusion</td>
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<td>Duration of illness prior to admission (days)</td>
<td>30</td>
<td>16</td>
<td>30</td>
<td>30</td>
<td>5</td>
<td>150</td>
<td>17</td>
<td>20</td>
<td>30</td>
<td>7</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Final outcome</td>
<td>Stuporous, against advice</td>
<td>Refer</td>
<td>Refer</td>
<td>Lost to follow up</td>
<td>Refer</td>
<td>Refer</td>
<td>Lost to follow up</td>
<td>Improve</td>
<td>Stuporous, against advice</td>
<td>Improve</td>
<td>Refer</td>
<td>Improve</td>
</tr>
<tr>
<td>Other site of infection</td>
<td>Lung mass</td>
<td>Spinal cord</td>
<td>Lung mass</td>
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<td>CSF findings</td>
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<td></td>
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<td>White blood cell count (cells/mm³)</td>
<td>162</td>
<td>35</td>
<td>400</td>
<td>0</td>
<td>149</td>
<td>40</td>
<td>50</td>
<td>25</td>
<td>150</td>
<td>400</td>
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<td>Cell predominance</td>
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<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
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<tr>
<td>Protein (mg/dl)</td>
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<td>293</td>
<td>139</td>
<td>308</td>
<td>206</td>
<td>70</td>
<td>326</td>
<td>32</td>
<td>186</td>
<td>56</td>
<td>98</td>
<td>67</td>
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<td>Sugar (mg/dl)</td>
<td>27</td>
<td>5</td>
<td>6</td>
<td>29</td>
<td>9</td>
<td>86</td>
<td>61</td>
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<td>India ink test</td>
<td>Not done</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
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</tr>
<tr>
<td>Cryptococcal antigen titer</td>
<td>Not done</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
<td>&lt;1:10</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
</tr>
<tr>
<td>Fungal Culture</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>Not done</td>
<td>positive</td>
<td>hypodense lesion</td>
<td>positive</td>
<td>hypodense lesion</td>
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<td>hypodense lesion</td>
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<td>hypodense lesion</td>
</tr>
<tr>
<td>CT brain</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Not done</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
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</tr>
</tbody>
</table>

Cryptococcal meningitis

variety gattii. In our series, there was one case of cryptococcoma of the spinal cord and one of cryptococcoma in the lungs, but identification of the variety could not be complete in our laboratory. Dissemination in the bloodstream is not common in patients without HIV infection, with 13-14% of cases being detected. In contrast, cryptococcemia is found in 66.7% of HIV-infected patients with cryptococcal meningitis.

Our findings were similar to those in studies involving patients not infected with HIV (Table 4). The clinical presentations including fever, headache, and signs of increased intracranial pressure were similar in these studies. Signs of meningeal irritation were found in 25-70% of the patients, whereas the India ink test was positive in about half of the patients.

All patients were treated with amphotericin B. Insertion of the ventriculoperitoneal (VP) shunt was performed in 2 cases. The indication was hydrocephalus in one case (case 9), and persistently increased CSF pressure in another (case 10).

Conclusion

Cryptococcal meningitis is not uncommon. The clinical presentation in patients not infected with HIV is somewhat similar to that in HIV-infected patients. However, in the latter group of patients the CSF white blood cell count is usually lower and the India ink test is more commonly positive. Cryptococcoma is a rare presentation and usually found in patients not infected with HIV. Our study had the draw-
backs of using retrospective data, an inadequately small sample size and incomplete medical records. A further well-designed study should be conducted.

References
รายงานผู้ป่วยที่มีสมองอักเสบจากเชื้อราคริปโตค็อกคัสที่ไม่ได้ติดเชื้อไวรัสเอชไอวี | ในโรงพยาบาลมหาราชนครเชียงใหม่

ชมรมวิจัยด้านสุขภาพและโรคติดต่อ | คณะแพทยศาสตร์ | มหาวิทยาลัยเชียงใหม่

บทคัดย่อ: ผู้วิจัยได้ทำการรวบรวมข้อมูลแบบย้อนหลังในผู้ป่วยโรคเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตค็อกคัสในผู้ป่วยที่ไม่ได้ติดเชื้อไวรัสเอชไอวีที่โรงพยาบาลมหาราชนครเชียงใหม่ตั้งแต่เดือนมกราคม พ.ศ. 2540 ถึงเดือนธันวาคม พ.ศ. 2546 เพื่อศึกษาอาการและอาการแสดงทางคลินิก ผลการตรวจทางห้องปฏิบัติการ และการรักษา พบว่าผู้ป่วยที่ได้รับการวินิจฉัยเป็นเชื้อราคริปโตค็อกคัส มีอาการที่พบบ่อยที่สุดคือไข้และปวดศีรษะ ที่พบได้ร้อยละ 50 ของผู้ป่วย การตรวจไขสันหลังโดยวิธี India ink ให้ผลบวกในผู้ป่วย 11 ราย จากการส่งตรวจทั้งหมด 11 ราย ผู้ป่วยทุกรายได้รับการรักษาด้วย Amphotericin B มีผู้ป่วยเสียชีวิต 2 ราย ด้วยระดับความรู้สึกตัวลดลงตั้งแต่เข้ารักษา.

คำสำคัญ: Cryptococcal meningitis, non-HIV infected patients