Bacterial meningitis in HIV-infected patients: Case reports and review of the literature

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R TOMMASINI, IW FONG. Bacterial meningitis in HIV-infected patients: Case reports and review of the literature. Can J Infect Dis 1992;3(2):71-74. Meningitis is not an uncommon complication of the acquired immune deficiency syndrome. Purulent meningitis is not a well recognized infection in human immunodeficiency virus (HIV) positive patients. Three cases of bacterial meningitis caused by *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Listeria monocytogenes* are presented. These cases illustrate that common community organisms may present in HIV positive patients. An acquired B cell defect may predispose to bacterial infections responsible for meningitis in HIV-infected patients.

Key Words: Bacterial infections, Human immunodeficiency virus, Meningitis

La méningite bactérienne chez les patients VIH positifs: Observations et tour d'horizon de la littérature

RESUME: La méningite n'est pas une complication rare du syndrome d'immunodéficience acquise. La méningite purulente n'est pas une infection bien reconnue chez les patients porteurs du virus de l'immunodéficience humaine (VIH). Trois cas de méningite bactérienne attribuables à *Streptococcus pneumoniae*, à *Neisseria meningitidis* et à *Listeria monocytogenes* sont présentés. Ils démontrent que les infections extra-hospitalières banales peuvent se manifester chez les patients VIH positifs. Il se pourrait qu'une anomalie des lymphocytes B prédispose le patient séropositif aux infections bactériennes responsables de la méningite.

USUAL CAUSES OF MENINGITIS IN SEROPOSITIVE HUMAN immunodeficiency virus (HIV) infected patients often include opportunistic infections. Defective T cell-mediated immunity is generally believed to lead to greater susceptibility to viral, fungal and parasitic diseases and certain bacterial infections. There have been several reports of defective B cell responses in acquired immune deficiency syndrome (AIDS) patients (1-5). One study concluded that pneumococcal infections are very common in patient with AIDS (6). There are no reported cases of neisseria meningitis in HIV-infected patients. This report examines three presentations of bacterial meningitis in patients with AIDS.

CASE ONE

A 23-year-old heterosexual Caucasian male had been diagnosed with severe hemophilia A at six months of age. Past medical history included an intracranial bleed at three years of age, accompanied by behavioral changes. He was tested and found to be positive for HIV four years prior to admission and his general state of health was good prior to admission. The patient was brought to emergency after being found confused, shivering and unable to respond appropriately. He had complained of a headache for three days prior to admission. There was no recent weight loss over the preceding months, nor was there a recent episode of

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Received for publication December 19, 1990. Accepted April 16, 1991

hemarthrosis. There was no history of intravenous drug use but the patient had abused cocaine. He had received transfusions of factor VIII for numerous episodes of small hemarthroses in the late 1970s and early 1980s.

On examination the patient was delirious and appeared toxic. His temperature was 39.8°C, pulse 108 beats/min, and respirations 48/min. Blood pressure was 156/98 mmHg. The patient was unable to respond to verbal commands. His eyes opened spontaneously and they were conjugately deviated to the right. He responded to pain and moved all limbs spontaneously. He appeared irritable. There was nuchal rigidity and positive Kernig's and Brudzinski's signs. There was no petechial or papular rash.

Computed tomography (CT) scan of the head on initial examination revealed a low density lesion at the left middle cranial fossa consistent with an arachnoid cyst. No enhancing mass lesion or hemorrhage was identified.

White blood cell count was $13.3 \times 10^9/L$ with 80% neutrophils, 4% lymphocytes and 8% monocytes. Prothrombin time was 13.4 s, partial thromboplastin time 78.6 s, and factor VIII level was 1%. The patient was given dexamethasone 10 mg and phenytoin 1 g intravenously. Factor VIII (6000 units) was given prior to lumbar puncture. At the time of the lumbar puncture, 20% mannitol was initiated. The patient's cerebrospinal fluid was cloudy, with protein 1.5 g/L and glucose 0.8 mmol/L (6.4% of serum value). Cerebrospinal fluid white cell counts were not available due to the presence of clots, but the differential cell counts were 85% neutrophils and 15% lymphocytes.

Cerebrospinal fluid Gram stain demonstrated many Gram-positive diplococci. The CD4/CD8 (T helper/T suppressor [T_H/T_S]) ratio was 0.14 (normal 0.8 to 2.5), the CD4+ cell count was 7% (normal 31 to 49) ($37 \times 10^6/L$ [normal 425 to 1050]).

The patient was treated with intravenous penicillin G 24 million units per day. The cerebrospinal fluid and blood grew *Streptococcus pneumoniae* sensitive to penicillin. His recovery was complicated by respiratory arrest requiring intubation and mechanical ventilation, and left lower lobe pneumonia. Recovery was further complicated by bilateral sensorineural deafness and neurogenic urinary retention remaining after successful treatment of meningitis and pneumonia.

CASE TWO

A 24-year-old homosexual Caucasian male diagnosed as HIV infected two years prior to admission presented to emergency with a painful left ankle. The patient appeared awake, alert and oriented. He complained of fever and chills. His history was initially negative for ankle trauma or swelling, rash, headache, photophobia or neck stiffness. Blood cultures were drawn and the patient left the emergency room. Cul-

tures were positive for Gram-negative diplococci. The patient was recalled to emergency and was found to have neck stiffness. He subsequently became obtunded. There was no recent history of weight loss. He had no history of intravenous drug abuse or transfusions. There was a history of penicillin allergy.

On examination the patient was obtunded but appeared well nourished. He was photophobic and agitated by light. He was unable to respond to verbal commands. His eyes opened spontaneously but did not fixate on any object. His temperature was 38.4°C, pulse 94 beats/min, and respirations 18/min. Blood pressure was 130/70 mmHg. He responded to pain with withdrawal. Fundoscopic examination was negative for papilledema. Kernig's sign was positive. There was bilateral cervical lymphadenopathy and nuchal rigidity. A petechial rash was present over the abdomen. The left ankle appeared unremarkable. CT scan of the head was normal, as was a chest radiograph.

White blood cell count was $13.4 \times 10^9/L$ with 87% neutrophils, 6.5% lymphocytes and 5.6% monocytes. Platelet count was $142 \times 10^9/L$ and erythrocyte sedimentation rate 64 mm/h. Prothrombin time was 14.4 s and partial thromboplastin time 35.8 s. Blood cultures were positive for *Neisseria meningitidis*. The CD4/CD8 (T_H/T_S) ratio was 0.34 and the CD4+ cell count was 20% or $282 \times 10^6/L$. The patient was treated with intravenous chloramphenicol and recovery was uncomplicated.

CASE THREE

A 29-year-old male with seroconversion for HIV four years earlier was admitted complaining of crampy abdominal pain about the epigastrium radiating to his left flank. The pain began two days prior to admission and was worsened by movement and eating. Nausea was an associated finding. There was no vomiting, diarrhea or melena on admission. The patient discontinued his medication of clofazimine, cyclosporine, ethionamide and zidovudine with the onset of pain. He also complained of weakness, increasing cough and dyspnea. Allergies included sulpha and penicillin, manifested by a rash. Past history included pneumocystis pneumonia and disseminated *Mycobacterium avium intracellulare* infections.

On examination the patient was normotensive, afebrile and had normal pulse and respiratory rates. Head and neck examination was unremarkable on admission. The patient demonstrated abdominal left lower quadrant pain upon flexion of the hips. The chest was clear to auscultation. Abdominal examination revealed a tender liver edge with a total span of 12 cm in the right midclavicular line. Bowel sounds were normal. He was tender upon deep palpation in the para-umbilical region, and a definable tender mass was palpated over the left flank.

Abdominal three views revealed localized ileus with

nondistended small bowel and a few air-fluid levels. Abdominal ultrasound demonstrated an ill defined amorphous mass in the left para-aortic region measuring 9 cm in diameter consistent with enlarged lymph nodes.

White blood cell count was $7.8 \times 10^9/L$ with 82% neutrophils, 16% lymphocytes and 2% monocytes. Hemoglobin was 72 g/L and platelet count $1.23 \times 10^9/L$. Serum electrolytes revealed borderline hyponatremia at 132 mmol/L upon admission which later decreased to 113 mmol/L during the course of the illness. The CD4/CD8 (T_H/T_S) ratio was 0.08, and the CD4+ cell count was 6% or $61 \times 10^6/L$.

The patient deteriorated after admission complaining of headache and vomiting. He became pyrexial, and antibiotics beginning with tobramycin and clindamycin were started after blood cultures were drawn. Blood cultures yielded Gram-positive bacilli. Lumbar puncture was performed with an opening pressure of 25 cmH₂O. Cloudy cerebrospinal fluid was obtained with glucose 0.4 mmol/L (serum glucose of 5.6 mmol/L), and a white cell count of $252 \times 10^6/L$. The differential cerebrospinal fluid cell counts were 88% neutrophils and 11% lymphocytes.

Blood cultures and cerebrospinal fluid grew *Listeria monocytogenes*. The patient had a negative skin test to penicillin and was started on intravenous ampicillin and gentamicin. His mental status deteriorated initially and then returned to normal with gradual correction of serum sodium. The patient completed 10 days of antibiotics but developed a generalized pruritic erythematous rash after stopping ampicillin. He was treated satisfactorily with antihistamines.

LITERATURE SEARCH

A literature search was carried out of on-line MEDLINE and AIDSLINE databases by computer search, references from abstracts from the Vth international conference on AIDS, textbooks and journals. Key words included 'bacterial infections', 'meningitis' and 'HIV'. The general literature on bacterial meningitis and HIV was also reviewed.

DISCUSSION

Causes of meningitis in seropositive HIV patients include cryptococcus, HIV, tuberculosis, syphilis, coccidioidomycosis and lymphoma (7,8). A search of the English literature found only two reported cases of pneumococcal meningitis in HIV-infected patients (6,10). Simberkoff and associates (6) have reported that *Strep pneumoniae* infection is very common among patients with AIDS. Bacteremic *Strep pneumoniae* disease occurs more frequently in HIV-infected patients without symptoms of AIDS or AIDS-related complex than in symptomatic cases; consequently, pneumococcal bacteremia is postulated to be an important first indicator of HIV infection (11).

Strep pneumoniae accounts for 10 to 15% of all cases of reported bacterial meningitis in the United States. Estimates of incidence from community-based studies range from 1.2 to 2.8 cases per 100,000 persons per year in the United States. It is seen primarily in young children, particularly children younger than two years of age, and it is the most common cause of bacterial meningitis in adults over 60 years of age (12).

Meningococcal meningitis accounts for about 20 to 30% of all reported cases of bacterial meningitis in the United States. The overall incidence estimated from community-based studies ranges from 0.18 to 9.2 cases per 100,000 persons per year (12). *L. monocytogenes* is an infrequent cause of meningitis – approximately 2% of all reported cases in the Centers for Disease Control study from 1978-81 (13). The estimated incidence in this population was 0.04 cases per 100,000 persons per year (12). Listerial meningitis occurs in neonates and in adult populations with immunosuppression, alcoholism and diabetes mellitus. *L. monocytogenes* is also a common cause of bacterial meningitis in renal transplant patients.

It was not unexpected in the present study to find *L. monocytogenes* in AIDS patients, but it is surprising that more cases are not reported. The incidence of listeriosis in patients with AIDS or at risk for HIV has increased compared to the non-HIV and nonrisk groups in New York City from 1981 to 1988. Listerial meningitis in New York City was identified in three of 11 patients (27%) with listeriosis who were HIV-infected or at risk for HIV (14). A recent review of 20 cases of listeriosis in HIV-infected patients described nine patients with meningitis and one with brain abscess (15). There was no reported case of neisseria meningitis in HIV-infected patients, although instances of *N. meningitidis* bacteremia have been reported (16).

Recent studies report the importance of bacterial infections particularly in the pediatric population. A prospective study in African children found that bacteremia was a predictor of HIV infection, with 44% seropositivity in the bacteremic group versus 19% seropositivity in the culture negative group (17). Group B streptococcal meningitis has been identified in two of 200 (1.0%) HIV-infected American children diagnosed at the University of Maryland and the New York University Medical Center, with infection occurring beyond the usual age of onset in these children (18).

Severe meningitis from encapsulated organisms such as *Strep pneumoniae*, *N. meningitidis* and *Haemophilus influenzae* could result from a lack of activation of B cells by capsular antigens in patients with AIDS (1,2). Investigations of B cell function in patients with AIDS have shown significantly lower antibody levels to polysaccharide and protein antigens after immunization with pneumococcal polysaccharide and protein antigens (1). A possible mechanism of meningitis in HIV-infected patients could relate to

abnormalities in intrinsic B cell physiology and a lack of CD4+ T helper cells in initiating specific antibody production. In affected adults, serum levels of IgG, IgA and IgD have been reported to be increased whereas IgM is relatively normal (2-5).

The primary differential diagnosis considered by clinicians in HIV-infected patients presenting with an altered mental state includes cryptococcal meningitis, central nervous system toxoplasmosis, central nervous system lymphoma, neurosyphilis, cytomegalovirus encephalitis, progressive multifocal leukoencephalopathy, and HIV encephalopathy. However, bacterial meningitis may be more prevalent in HIV-infected patients than previously realized. It is very possible that there is under-reporting of bacterial meningitis in HIV patients as these microorganisms are well recognized causes of meningitis even in healthy adults within the same age group. It is also possible that the cases of pneumococcal and meningococcal meningitis occurring

in HIV patients occurred by chance with no increased predisposition due to HIV status. The occurrence of pneumococcal or *H influenzae* sepsis is not reportable which makes estimation of the expected incidence rates in HIV-infected groups unreliable.

The occurrence of the three present cases of bacterial meningitis in HIV-infected patients at one institution over one year suggests that bacterial meningitis may be more prevalent in HIV-infected patients than previously realized. Prospective studies of the incidence of bacterial meningitis are needed for a larger population in both HIV and non-HIV groups to obtain an accurate estimate of disease incidence and to control for other unrecognized factors affecting this hypothesis. However, if a higher incidence of bacterial meningitis in the HIV-infected group is demonstrated, a higher suspicion of bacterial meningitis will be required in HIV-infected patients after cryptococcal meningitis is ruled out.

REFERENCES

1. Ammann AJ, Schiffman G, Abrams D, Volberding P, Ziegler J, Conant M. B-cell immunodeficiency in acquired immune deficiency syndrome. *JAMA* 1984;251:1447-9.
2. Lane HC, Masur H, Edgar LC, Whalen G, Rook RH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;309:453-8.
3. Ammann AJ, Abrams D, Conant M, et al. Acquired immune dysfunction in homosexual men: Immunologic profiles. *Clin Immunol Immunopathol* 1983;27:315-25.
4. Chess G, Daniels J, North E, Macris NT. Serum immunoglobulin elevation in the acquired immunodeficiency syndrome (AIDS): IgG, IgA, IgM, and IgD. *Diagn Immunol* 1984;2:148-53.
5. Papadopoulos NM, Frieri M. The presence of immunoglobulin D in endocrine disorders and diseases of immunoregulation, including the acquired immunodeficiency syndrome. *Clin Immunol Immunopathol* 1984;32:248-52.
6. Simberkoff MS, El Sadr W, Schiffman G, Rahal JJ Jr. *Streptococcus pneumoniae* infections and bacteremia in patients with acquired immune deficiency syndrome, with report of a pneumococcal vaccine failure. *Am Rev Respir Dis* 1984;130:1174-6.
7. Kovacs JA, Masur H. Opportunistic infections. In: Devita VT, Hellman S, Rosenberg SA, eds. *AIDS, Etiology, Diagnosis, Treatment and Prevention*, 2nd edn. Philadelphia: JB Lippincott Co, 1988:199-225.
8. Pons VG, Jacobs RA, Hollander H. Non-viral infections of the CNS in patients with acquired immunodeficiency syndrome. In: Rosenblum ML, Levy RM, Bredesen DE, eds. *AIDS and the Nervous System*, 1st edn. New York: Raven Press, 1988:263-83.
9. Zuger A, Louie E, Holzman RS, Simberkoff MS, Rahal JJ. Cryptococcal disease in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;104:234-40.
10. Havlir DV, Witt MD, Sande M. A 32-year-old man with the acquired immunodeficiency syndrome and pneumococcal meningitis. *West J Med* 1987;146:618-61.
11. Dobkin J, Mandell W, Sethi N. Bacterial pneumococcal disease as the first manifestation of human immunodeficiency virus (HIV) infection in adults. Ottawa: International Development Research Centre. Vth International Conference on AIDS, Montreal, 1989;5:233. (Abst MBP71)
12. Bolan GB, Barza M. Acute bacterial meningitis in children and adults. *Med Clin North Am* 1985;69:231-40.
13. Schech WF, Ward JI, Band JD, Hightower A, Fraser DW, Broome CV. Bacterial meningitis in the United States 1978 through 1981. *JAMA* 1985;253:1749-55.
14. Kales CP, Holzman RS. Listeriosis in patients with HIV infection. Ottawa: International Development Research Centre. Vth International Conference on AIDS, Montreal, 1989;5:234. (Abst MBP77)
15. Berenguer J, Solera J, Diaz MD, Moreno S, Lopez-Herce JA, Bousa E. Listeriosis in patients infected with human immunodeficiency virus. *Rev Infect Dis* 1991;13:115-9.
16. Aguado JM, Vada J, Zuniga M. Meningococcemia: An undescribed cause of community-acquired bacteremia in patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *Am J Med* 1990;88:314.
17. Lepage P, Van de Perre P, Nsengumuremyi F, Van Goetliem C, Bogaerts J, Hitimana DG. Bacteremia as predictor of HIV infection in African children. *Acta Paediatr Scand* 1989;78:763-6.
18. Di John D, Johnson JP, Lawrence R, Schieken LS, Rennels MB. Very late onset of group B streptococcal sepsis in infants with HIV infection. Ottawa: International Development Research Centre. Vth International Conference on AIDS, Montreal, 1989;5:330. (Abst TBP262)