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Acute recurrent lymphocytic meningitis in an immunocompetent HIV-positive African woman: Is it a Mollaret's meningitis or not?

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Abstract

We report a case of acute recurrent meningitis in an HIV-positive immunocompetent woman. In this case, a 34-year-old African woman with a known HIV infection presented with symptoms of acute meningitis. She was on combination antiretroviral therapy with abacavir, lamivudine, and nevirapine. Her HIV RNA level was <70 IU/mL, and CD4 counts were 640 cells/mm^3. This indicates that she was not immunocompromised. She was febrile on examination, with marked neck stiffness. Her cerebrospinal fluid revealed raised white cell counts with 100% lymphocytes and mildly raised protein. Polymerase chain reaction confirmed herpes simplex type 2 meningitis. She recovered fully with aciclovir 800 mg three times a day. However, she was readmitted with a similar presentation 5 months after the initial admission. Her cerebrospinal fluid confirmed recurrent herpes simplex type 2 meningitis. This case alerts the profession to the possibility of non-opportunistic infections in an immunocompetent HIV-positive patient and of herpes simplex virus type 2 causing recurrent lymphocytic meningitis.

Keywords

Acute viral meningitis, HIV/AIDS, herpes simplex virus type 1 and 2, enteroviruses, recurrent lymphocytic meningitis

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Introduction

Meningitis in HIV-positive patients is multifactorial. HIV itself causes aseptic lymphocytic meningitis, which usually occurs during primary HIV infection.

Meningitis is typically due to an infection and can be caused by viruses, bacteria, and fungi. Fungal meningitis, usually due to *Cryptococcus neoformans*, is frequently seen in immunocompromised patients with CD4 counts of less than 350 cells/mm^3. Our patient's CD4 counts were over 600 cells/mm^3. Mollaret's meningitis is typically benign recurrent lymphocytic meningitis. Although the cause of Mollaret's meningitis was not known for a long period of time, recent development of molecular technology identified the cause to be herpes simplex virus type 2.

Case report

A 34-year-old African woman was diagnosed with HIV infection when she attended for sexually transmitted infection screen in 2006. She was commenced on abacavir, lamivudine, and nevirapine, as her nadir CD4 count was 90 cells/mm^3. Her last HIV RNA level was <70 IU/mL, and CD4 counts were persistently over 600 cells/mm^3. She had a history of recurrent painful vulval ulcers. Her last documented clinical episode of genital herpes was in 2014. However, the vulval swab for the polymerase chain reaction (PCR) of herpes simplex virus (HSV) DNA 1 and 2 were negative.

In May 2016, she was admitted to a medical admission unit with a 4-day history of fever, headache with neck pain, and intolerance to light. She did not give any history of

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recent clinical features of mucocutaneous herpes infection. She did not have any previous history of viral meningitis. She was born in Kenya and living in the United Kingdom for 26 years. She had been to Kenya 3 years prior to her hospital admission on holiday. Examination revealed marked neck stiffness, with positive Kernig's sign. Her temperature was 38.7°C. She was alert with a Glasgow Coma Scale (GCS) of 15/15. There were no focal neurological signs.

Investigations showed that her total white blood cells were 5.7×10^9/L, with neutrophils of 3.0×10^9/L. C-reactive protein (CRP) was <5 mg/L. Blood cultures were sterile. Chest radiograph and computed tomography (CT) of the head were reported as normal. Cerebrospinal fluid (CSF) analysis showed total white blood cells of 396×10^6/L, with 100% of lymphocytes and raised CSF protein of 0.88 g/L. The Gram stain did not show any organisms. Serum glucose was 5.1 mmol/L with CSF glucose of 2.9 mmol/L. She was treated with intravenous aciclovir, 800 mg three times a day, and cefotaxime 2 g stat. Her weight was 82.3 kg. Subsequent CSF PCR for herpes simplex type 2 DNA was positive. Herpes simplex type 1 DNA, meningococcal DNA, pneumococcal DNA, and enterovirus DNA were all negative. Cefotaxime was stopped. She was discharged home 3 days after intravenous aciclovir. She was given a 2-week course of oral valaciclovir, 1 g three times a day.

She was reviewed at an outpatient clinic a week later. She remained asymptomatic. She had been advised about the possibility of similar illnesses recurring and reminded to seek medical advice promptly.

She was readmitted with a similar illness 5 months after her last admission. She was alert with GCS of 15/15. She had neck stiffness. Her CD4 counts were 612 cells/mm^3. Her repeat CSF showed white blood cell counts of 151/10^6/L with 90% lymphocyte count and raised protein of 0.66 g/L. Herpes simplex type 2 DNA was detected; by contrast, Herpes simplex type 1 DNA, meningococcal DNA, pneumococcal DNA, and enterovirus DNA were all negative. CSF HIV RNA level was not done.

Discussion

Meningitis is typically due to an infection and can be caused by viruses, bacteria, and fungi. Fungal meningitis, usually due to *Cryptococcus neoformans*, is frequently seen in immunocompromised patients with CD4 counts of less than 350 cells/mm^3. Our patient, with a CD4 count of over 600 cells/mm^3, is not considered to be an immunocompromised host. The most common causes of viral meningitis in the United Kingdom are enteroviruses and herpes viruses. These enteroviruses include coxsackie viruses, echoviruses, polioviruses, and numbered enteroviruses. Among enteroviruses, coxsackie viruses and echoviruses are the commonest causes of acute meningitis. One study from the United Kingdom showed non-polio enteroviruses accounting for 46% followed by herpes simplex type 2 (31%), varicella zoster virus (11%), and herpes simplex virus type 1 (4%).[1] In another study, including four sets of primers such as enterovirus, herpes simplex virus, varicella zoster virus, and Epstein–Barr virus accounted for 96% of the positive PCR results in the United Kingdom.[2] Therefore, PCR of CSF is the gold standard for diagnosing the causative agent in viral meningitis.[3]

As in our case, viral meningitis is strongly suggested by the combination of raised white cell counts with a predominance of lymphocyte cells, mildly raised protein (up to1 g/L), and a normal ratio of glucose in CSF:blood (>50%) in CSF.[4] Other causes of lymphocytic meningitis include *Mycobacterium tuberculosis, Listeria monocytogenes*, HIV seroconversion, and partially treated bacterial meningitis.

Our patient had CT of the head prior to her lumbar puncture, even though she was considered to be an immunocompetent host due to her CD4 count of more than 600 cells/mm^3. A head CT is indicated before a lumbar puncture in the following conditions: focal neurological signs, papilloedema, low GCS, new onset of seizures, and also for immunocompromised patients due to HIV or immunosuppressive drugs.[5]

Although HSV-2 can cause herpes meningitis in men, it is much more common in sexually active women. As in our patient, HSV-2 commonly causes meningitis, whereas HSV-1 tends to cause encephalitis.[6] Many patients with HSV-2 meningitis do not have a concurrent history of genital or labial herpes.[7] Although our patient had a history of genital herpes, she did not have any concurrent clinical evidence of such episode. HSV-2 is the most common cause of recurrent lymphocytic meningitis and is responsible for 84% of recurrent meningitis.[6] Recurrent idiopathic aseptic lymphocytic meningitis is known as Mollaret's meningitis.[8]

With the increased use of PCR tests, it is now believed that recurrent aseptic lymphocytic meningitis is predominantly caused by herpes simplex type 2 infection.[9] The term "Mollaret's meningitis" should be reserved for idiopathic cases of recurrent aseptic lymphocytic meningitis. A double-blind randomized controlled trial with a long-term suppressive therapy with valaciclovir 500 mg twice a day did not show any benefit in the prevention of recurrent episodes of HSV-type 2 meningitis.[10]

It is important to clinically differentiate encephalitis from meningitis, since the prognosis and treatments differ. Encephalitis is strongly suggested by the change or personality, behavior, and level of consciousness, as well as by focal neurological signs and seizures.[11] Our patient, however, did not have any of those features; she only displayed features of meningitis. HSV encephalitis is treated with intravenous aciclovir 10 mg/kg three times a day for 2–3 weeks. Our patient had intravenous aciclovir for 3 days only; following the result of positive HSV-2 in the CSF, the treatment was changed to oral valaciclovir 1 g, three times a day for 2 weeks. She was then advised to take aciclovir 400 mg twice a day for a longer period.

Opportunistic infections, such as cryptococcal and tuberculous meningitis, should be considered in HIV-positive patients with a CD4 count of less than 350 cells/mm^3.[12] Our

patient's CD4 count was persistently over 600 cells/mm^3. Therefore, this type of patient should be treated as immunocompetent and non-opportunistic infections should be considered as a cause of meningitis.

Learning points

- HSV-2 typically causes meningitis, whereas HSV-1 frequently causes encephalitis.
- HSV-2 is the most common cause of recurrent lymphocytic meningitis.
- Non-opportunistic infections causing meningitis should be considered first in HIV-positive patients with normal CD4 counts of over 500 cells/mm^3.

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Informed consent

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