CASE REPORT

Unravelling the Gordian knot: diagnostic dilemma in an HIV-positive patient with neurological involvement

Avirup Chakraborty,¹ Sattik Siddhanta,² Kuntal Bhattacharyya,² Amit Das,²
Siwalik Banerjee,² Rathindra Nath Sarkar,² Utpal Kumar Datta,²
Nilanjan Chakraborty¹

¹ICMR Virus Unit, Kolkata, ID & BG Hospital, Kolkata, West Bengal, India

²Department of Medicine, Calcutta Medical College and Hospital, Kolkata, West Bengal, India

Correspondence to

Dr. Nilanjan Chakraborty;
nilanjan.chakraborty@ymail.com

SUMMARY

We report a case of a 40-year-old seropositive-HIV patient with a CD4 count of 120 who presented with fever, severe headache and neck stiffness. Suspecting a case of tubercular meningitis (TBM; as tuberculosis is the commonest opportunistic infection in HIV/AIDS patients in India), a lumbar puncture was performed and a cerebrospinal fluid study revealed TBM. The patient was started on combination antitubercular drug therapy from directly observed treatment, short course (DOTS) (Cat 1 regimen) along with pyridoxine 40 mg/day and adjunctive corticosteroid therapy. However, despite adequate antitubercular therapy for 4 weeks, the patient did not show any improvement in his clinical condition. On the contrary, in the process he developed cytomegalovirus (CMV) retinitis. So we question our learned readers if the coinfection of *Mycobacterium tuberculosis* and CMV should be implicated for the failure to respond to isolated antitubercular therapy contrary to our expectation.

BACKGROUND

Tuberculosis (TB) still remains one of the leading causes of infection-related mortality worldwide. According to the World Health Organization (WHO), in the year 2009, 1.7 million people died from TB. WHO estimates that there was a fall in the global incidence of TB to 137 cases per 100 000 population in 2009 from 142 cases per 100 000 population in 2004, but the rate of fall is very slow.¹ Dual infection with HIV and *Mycobacterium tuberculosis* was estimated in 380 000 people in 2009, as obtained from the latest reports on TB/HIV facts 2011 from WHO.¹ Studies report that HIV-positive individuals have an increased risk of developing TB in case of *M tuberculosis* infection as a result of immunosuppression by the virus, thus leading to greater rates of progression of latent or recent *M tuberculosis* infections in HIV-infected individuals.² WHO estimates that HIV infection increases the risk of TB by 20–37-fold.³

TB may also involve the central nervous system (CNS). The primary clinical manifestations of CNS TB are a consequence of the inflammatory response to invasion by *M tuberculosis*. This may lead to hydrocephalus and vasculitis, which contributes to infarction, causing a potentially irreparable neurological damage.⁴ CNS TB generally involves meninges causing meningitis, tuberculous granulomas (tuberculomas) or tuberculous brain abscess.⁵ Meningitis is the most devastating manifestation of

TB infection in the CNS. A case series from the USA reveals that 17% of patients with tubercular meningitis (TBM) died during the first 9 months of therapy.⁶ TBM is often associated with the development of multiple life-threatening neurological sequelae. When allowed to progress without treatment, it may lead to coma and may progress to death.⁷

Other than TB, in case of HIV/AIDS patients, cytomegalovirus (CMV) is associated with causing a wide range of clinical manifestations in the CNS. This virus (CMV) also plays extensive roles in morbidity and mortality among this patient population. The neurological involvement of CMV is very common among this group of patients and may lead to meningoencephalitis or ventriculitis, myelitis, polyradiculitis, polyneuropathy and retinitis.⁸

However, with the advent of highly active antiretroviral therapy (HAART), there has been a rapid decrease in the mortality rates and a better prognosis has been observed among patients with CMV disease.⁹ CMV retinitis is a very common ocular infection due to CMV infection among the AIDS patients, particularly in those with low CD4 counts.^{10–12} It causes necrosis of the entire retina, detachment of the retina, optic atrophy and loss of vision.¹³ Previous studies by Goldbeg *et al* have revealed that in the pre-HAART era, the estimated occurrence of CMV retinitis in patients with AIDS lies between 20% and 40%. In the post-HAART era, an 80% decrease in the incidence of retinitis among this patient group has been observed. In many cases, however, vitritis occurring as a consequence of a relapse in CMV retinitis has been reported.¹⁴ Retinitis affects 30% of the people suffering from AIDS.¹⁵ The associated symptoms and signs are fever, chills, fatigue, myalgia, motor deficits, sensory abnormalities, disorientation, confusion, unilateral or bilateral visual loss, urinary retention, constipation or coma.¹⁶

We report here a case of a 40-year-old HIV patient who presented with fever, severe headache and neck stiffness. He was later diagnosed with TBM. Despite adequate therapy, his clinical condition did not improve. He further developed CMV retinitis. Is this neurological involvement of CMV that is preventing the antitubercular therapy from acting making the scenario more complicated?

CASE PRESENTATION

A 40-year-old known HIV patient with a CD4 count of 120 was admitted in the Department of General Medicine Calcutta Medical College and Hospital,

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Kolkata, India. He presented with fever with an evening rise and severe headache, malaise, weight loss and neck stiffness. However, the patient denied having a history of any seizures or any history suggestive of any focal neurological deficit. The patient was also put on combination antiretroviral therapy which the patient discontinued after a few months, citing severe adverse effects, particularly gastrointestinal intolerance.

On presentation, the patient was suffering from significant weight loss, nausea and vomiting during this entire tenure of illness. He was also having dry cough, but expectoration, haemoptysis, chest pain or dyspnoea was absent. He was mildly febrile with a pulse rate of 112 beats/min and in whom mild pallor was present. Palpable lymphadenopathy was not detected on clinical examination. On neurological examination, both neck rigidity and Kernig's sign were positive but there was no evidence of any cranial nerve palsy at presentation.

Ophthalmoscopy revealed no papilloedema. A complete blood count showed the following findings: haemoglobin 8.1 g %, thin layer chromatography 4300, neutrophils 42, lymphocyte 56, eosinophil 1, monocyte 1, basophil 0. Fasting blood sugar 94, urea 38, creatinine 0.9. Other biochemical parameters, including liver function tests, were within normal limits.

Suspecting a case of TBM (as TB is the commonest opportunistic infection in HIV/AIDS patients in India), a lumbar puncture was performed and a cerebrospinal fluid (CSF) study revealed the following findings: CSF pressure was mildly increased; appearance was clear with no red blood cells in CSF; Cob Web Coagulum was absent; chemical examinations revealed—protein 375 mg/dl, sugar 30 mg/dl, chloride 580 mg/dl. A CSF viral study was carried out for the herpes simplex virus and Japanese B encephalitis virus, which turned out to be negative. Initial CSF viral tests did not include CMV as the patient's CD4 count was 120 at presentation and we hardly thought of CMV involvement at that juncture as CMV infection is especially common at CD4 below 100 (maximum cases at CD4 < 50) and also because the patient had no clinical signs and symptoms suggestive of CMV infection at that point.

Microscopic examination revealed total cells 450, polymorphs 8%, lymphocyte 92%. Adenosine deaminase value was 15.9 U/l (increased). Moreover, numerous acid fast bacilli were seen in the smear. Montoux test and CSF culture revealed *M tuberculosis*. Cryptococcal antigen (capsular antigen) in CSF came out as negative, thereby confirming our clinical diagnosis of TBM.

Neuroimaging (CT scan) revealed abnormal enhancement of the basal cisterns (this is not a case of raised intracranial tension). The case was diagnosed as TBM and the patient was started on combination antitubercular drug (ATD) therapy from DOTS (Cat 1 regimen) along with pyridoxine 40 mg/day and adjunctive corticosteroid therapy—Injection Dexamethasone (0.4 mg/kg/day)—with the plan of gradually tapering the latter over 4 weeks.

However, no improvement in the clinical condition of the patient was observed and his clinical status remained static despite adequate therapy for 4 weeks. However, to the contrary, his fever also relapsed. Meanwhile, the patient also complained of a progressive dimness of vision and blurring and appearance of floaters. Suspecting CMV retinitis, a funduscopy was performed which revealed an arcuate zone of perivascular haemorrhage with retinitis in the inferotemporal (figure 1). A blood sample of the patient was drawn which revealed IgG (4.95, positive > 1.1), IgM (1.9, positive > 1.1) and a CMV viral load of 2.1×10^5 copies of CMV DNA/ml serum. The patient's general condition was too poor to perform a repeat CSF study. The patient was started on oral valganciclovir (450 mg/day) to combat retinal involvement.

Figure 1 Cytomegalovirus retinitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of HIV-associated meningitis includes chronic paroxysmal hemicranias, meningococcal meningitis, migraine headache, neurosyphilis and staphylococcal meningitis. Other problems to be considered include lymphomatous meningitis, bacterial meningitis which often occurs in conjunction with sepsis, and CMV ventriculoencephalitis which usually results in a change in mental status that evolves over several weeks and can be misdiagnosed as HIV-associated dementia. In patients receiving HAART who have a syndrome of relapsing and remitting meningitis with negative cultures and atypical signs and symptoms, consider immune reconstitution inflammatory syndrome. This is regarded as an overactive response of a newly reconstituted immune system to infectious agents already present in the patient when therapy is started. In rare instances, metastatic CNS lymphoma can appear as meningitis. Brain abscesses as a result of various infective causes are other possibilities.

OUTCOME AND FOLLOW-UP

No improvement was observed in the clinical conditions of the patient.

DISCUSSION

The relative risk for the development of TB among the HIV/AIDS patients is quite high.¹⁷ HIV patients with active TB have an increased risk of developing extrapulmonary TB, and this risk enhances with a decline in the CD4 count making them more vulnerable towards TBM.¹⁸ An autopsy study carried out in Kenya revealed that disseminated TB was found in 41% of the HIV-infected TB patients compared with only 6% of the HIV uninfected TB patients.¹⁹ In another study carried out in Spain, 10% of the HIV-infected patients had a positive culture for *M tuberculosis* (CSF being the site for culture) compared with 2% of the HIV non-infected TB patients.²⁰

Several observational studies have compared the HIV-positive TBM death rates with those of the HIV-negative ones. A study by Thwaites *et al*²¹ concluded that HIV-infected adults in Vietnam revealed that this patient group were at risk for mortality at 9 months. Another study carried out among children in South Africa by van der Weert *et al*²² revealed that 8 of 34 HIV coinfecting children expired during the treatment period while all the 55 HIV non-infected ones survived. Each of these studies

thus concludes that HIV coinfection with TBM has a poor prognosis and may meet with adverse effects.

A study conducted by Katrak *et al*²³ in India concluded that 36% of the HIV-positive TBM adult patients expired during 6 months of TBM compared with only 10% of the non-HIV-infected ones. A recent study carried out by Bandyopadhyay *et al*²⁴ consisting of 82 TBM patients of Eastern India admitted in Nil Ratan Sarkar Hospital (a tertiary care hospital in West Bengal, Kolkata, India)—40 of whom were HIV positive—concluded that HIV-infected TBM patients were more likely to develop severe neurological complications. As one of the causes for this poor prognosis in TBM among this patient group, the authors have questioned the role of opportunistic infections along with the HIV complications like coexisting HIV encephalopathy and extensive vasculopathy.²⁴

Treatment for TBM in HIV-infected patients follows the same drug regimen as in the case of the HIV-uninfected individuals. The course should include rifampicin whenever possible and adjunctive corticosteroids are recommended for the HIV-infected ones. However, our patient (in discussion) failed to respond satisfactorily despite adequate antitubercular therapy, and to add to the situation, he developed ophthalmological involvement of the CMV infection. Manifestations of CMV infections usually occur at CD4<50. However, as the patient discontinued HAART because of gastrointestinal side effects, it is expected that his CD4 count might have decreased considerably during this period.

Several extrinsic as well as intrinsic factors may be responsible for the failure in treating TBM with antituberculosis therapy. The important intrinsic factors that may be involved are the development of drug resistance (MDR or XDR TB) or drug toxicity, intolerance and bioavailability.²⁵ The role of coexisting diseases like diabetes mellitus, nutritional anaemia and alcoholic liver disease can also never be ruled out. Some of the important extrinsic factors involved may include: non-qualified and non-allopath physicians with limited knowledge about the multiple preparations, combination packs and dosages of the drugs to be prescribed. Moreover, illiteracy and poverty, especially among the patients of a developing country, are the greatest problems, resulting in the maximum cases of drug defaulters or loss to follow-up.

However, taking the aforementioned important factors into account, we can assertively claim that for the above patient none of these factors have played any role in the failure to respond to the antituberculosis therapy. The patient did not develop drug resistance, and nor was his therapy stopped midway due to the development of any drug toxicity or intolerance. The treatment that was being followed is recommended by WHO—so the questions of wrong treatment can be ruled out, and moreover, as his treatment for TB is supported by the Government, thus the issue of poverty can be ruled out also.

Usually, in any case of TBM, there is a noticeable amount of clinical improvement within two weeks of the start of ATD therapy, for example, decrease of headache and nuchal rigidity, subsidence of fever and a sense of general well-being among the patients. In our case, the patient hardly showed any clinical improvement—on the contrary, his condition worsened. As the patient was hospitalised, the patient was fully compliant with multidrug ATD therapy. The patient party showed the empty blister packs. Thus, we may assume that the patient was strictly adhering to the physician's advice. Moreover, the patient developed a somewhat orange discolouration of urine (a common side effect of rifampicin therapy), which confirms our belief that the patient was adherent to therapy. All these taken together

clearly confirm the failure of antimycobacterial agents to CNS TB, though the patient was highly adherent to the drug regimen. The fact that the patient was not receiving HAART may be an aggravating factor contributing to his non-improvement, but the lack of response to ATD therapy despite compliance to the drug regimen is presumed to be the pivotal cause. By any means, a gap of two weeks is usually maintained between anti-TB drugs and HAART.

The question thus arises, was there any comorbid disease that might have worsened the scenario?—the patient did not have diabetes or any other known comorbid disease (other than being HIV positive). The other comorbidities that could have influenced the outcome include cerebrovascular accidents because of tubercular arteritis leading to various neurological manifestations depending upon the vascular territory involved, seizures, hydrocephalus because of basal adhesions and multiple cranial nerve palsies. The patient did not have features of any of the above.

However, the development of CMV Retinitis during the course of the treatment has kindled the question among us whether the coinfection of *M tuberculosis* and CMV (neurological involvement) can be implicated as the cause of the patient's failure to respond to isolated antitubercular therapy contrary to our expectation.

Under this setting of such extreme immunosuppression (HIV infection with low CD4 count), CMV infection is extremely common among this group of patients. We thus enquire whether the coinfection of *M tuberculosis* and CMV can be implicated as the cause of the patient's failure to respond to isolated antitubercular therapy contrary to our expectation. Further research work is thus extremely essential to unfold this Gordian knot so as to reveal if indeed neurological involvement of CMV is responsible for the poor prognosis of TBM in the HIV-positive patients.

Learning points

- ▶ In case of HIV patients suffering from meningitis, detection of all the suspected pathogens should be made prior to the start of treatment to avoid further complications.
- ▶ Coinfection with cytomegalovirus (CMV) should always be suspected in those cases of meningitis that are not responding properly or failing to respond despite adequate therapy in immunocompromised patients.
- ▶ CMV infection leading to CMV retinitis is very common among AIDS patients. So in case of HIV-infected patients, ophthalmoscopic examination and stringent eye check-up must be a mandatory practice in virtually all HIV-infected patients, especially those with a low CD4 count.
- ▶ Bowen *et al* have reported that a positive-CMV PCR is significantly associated with CMV disease development among HIV/AIDS patients with a CD4 count <50 and can be used to target ophthalmological resources to those patients at highest risk of retinitis.²⁶ We thus suggest a regular check-up and proper monitoring of the CMV viral load for HIV/AIDS patients with a CD4 count<50 even if the patient negates any symptoms as asymptomatic patients who are PCR-positive represent a high-risk group.
- ▶ Further research work is thus extremely essential to unfold this Gordian knot so as to reveal if indeed neurological involvement of CMV is responsible for the poor prognosis of TBM in the HIV-positive patients.

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