

Difficulties with diagnosis and consequential poor outcome due to stigma of acquired immunodeficiency syndrome – a case report

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Low incidence of human immunodeficiency virus (HIV) infections and acquired immunodeficiency syndrome (AIDS) has been detected in Croatia so far. Toxoplasmic encephalitis (TE) is the most common opportunistic cerebral infection in AIDS patients and is highly responsive to antiparasitic chemotherapy, if treated at an early stage.

We present the case of the brain biopsy confirmed as TE on a 36-year-old female patient who at admission presented with unconsciousness and a right hemiplegia. A MSCT was performed and two hypodense lesions were diagnosed. The patient's family initially denied the presence or history of any medical problem or infection. An MRI showed multiple ring-enhanced mass lesions. An infectologist required a brain biopsy to exclude cerebral lymphoma and multiple metastases. Pathohistological analysis suggested TE. Meanwhile, patient's blood samples were found to be HIV positive. The patient was transferred to University Hospital for Infectious Diseases in Zagreb, where she died 2 days following admission. The patient's family terminally confessed that the patient had been HIV positive for 10 years and had refused any treatment. Family's denial of infection as well as 'hiding information' concerning patient's health from physicians involved in her treatment caused a delay in proper on-time patient treatment.

We would like to emphasize that TE must be considered as a differential diagnosis in patients presenting with multiple cerebral lesions, including patients without acknowledged past history of HIV infection. A stigma towards HIV infection and ignorance of the disease still exist and therefore hinders proper treatment.

Keywords: Human immunodeficiency virus (HIV), Toxoplasmosis, Multiple cerebral lesions

Introduction

Cerebral toxoplasmosis is one of the most common opportunistic neurological infections¹ and the most common cause of cerebral mass lesions in acquired immunodeficiency syndrome (AIDS) patients.²⁻⁴ If untreated, toxoplasmic encephalitis (TE) is uniformly fatal⁵ and a major cause of death in AIDS patients.⁶ Yet, effective anti-biotherapy capable of producing rapid remission of active infection is available, which must be continued throughout life to prevent recurrence.⁷ The clinical onset of TE may easily mimic other neurological diseases with focal neurological defects and headache,⁸ therefore, it must be considered in the differential diagnosis in patients with cerebral lymphoma, multiple metastasis tumour, or brain abscesses.^{3,9} Croatia is considered to have a low incidence of human immunodeficiency virus

(HIV) infection and AIDS. The average incidence rate of HIV infection in Croatia is 15.0 per million population.¹⁰ Low level of awareness of highly active antiretroviral therapy (HAART) and stigma associated with HIV infection, additionally hinder rapid diagnosis and proper treatment. This case report presents difficulties with diagnosis and consequential poor outcome caused due to stigma and family members' ignorance of AIDS.

Case Report

A 36-year-old homemaker, from a small village about 50 miles away from our capital city Zagreb, was presented to the Department of Neurology, unconscious with right hemiplegia. On the second day following admission, she developed a fever. At admission, a CT scan showed two hypodense lesions in the right frontal and left parietal lobe, described as possible vascular lesions. She had started treatment for immunothrombocytopenia and auto immune hemolytic anemia (AIHA) under a haematologist

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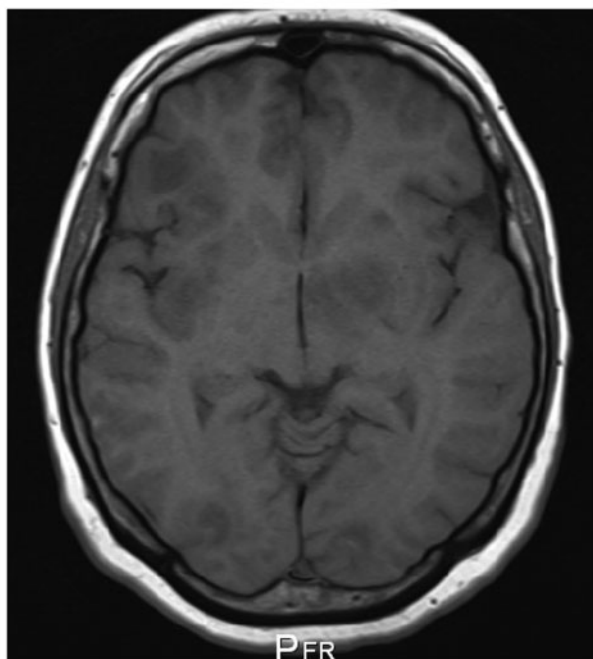


Figure 1 T1W MRI showing multiple lesions iso- to hypointense to grey matter.

8 months prior to admission. She had received Medrol 8 mg (methylprednisolone) 3 months ago. For the past 2 months, she had been suffering from headaches. Her family initially denied any history of medical problems, previous primary malignancy, or known infection. She had two children and no history of travel to endemic areas or any risk behaviour. We performed extensive immunological, haematological, and infectious examinations (flow cytometric immunophenotyping cerebrospinal fluid, serum protein electrophoresis, treponema pallidum hemagglutination assay, HIV test, function of the blood-brain

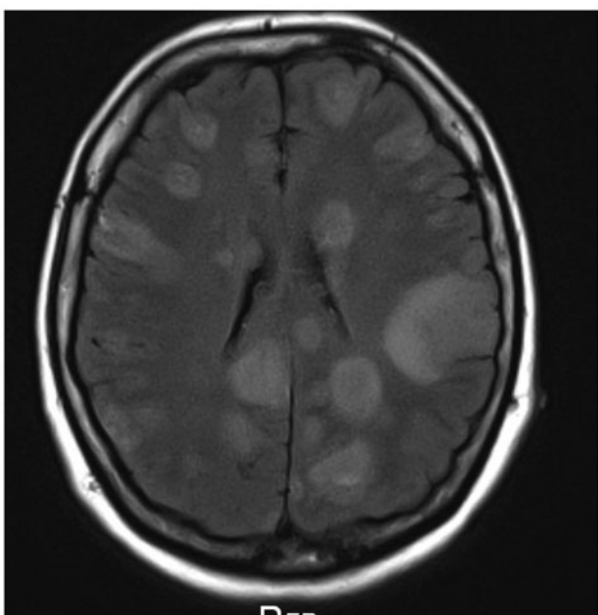


Figure 2 FLAIR (fluid-attenuated inversion recovery) MRI showing multiple lesions iso- to hyperintense to grey matter.

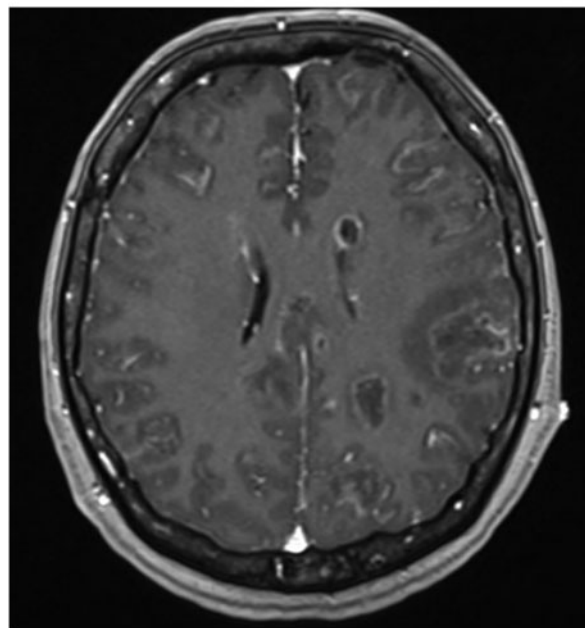


Figure 3 T1W MRI showing ring-enhanced mass lesions with IV gadolinium.

barrier, C3 and C4 complement, perinuclear anti-neutrophil cytoplasmic antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, cryoglobulin test, rheumatoid factor, and immunoglobulin M and G).

In the first analysis of cerebrospinal fluid, lymphocytosis and elevated protein level 1.4 g/l were diagnosed, and intravenous treatment was started with Acyclovir (acycloguanosine) and Ceftriaxone in the recommended dosage (Ceftriaxone 2 × 2 g IV, Acyclovir 3 × 500 mg IV). MRI showed multiple iso- to hypointense lesions to grey matter on unenhanced T1-sequences (Fig. 1), iso- to hyperintense to grey matter lesions on FLAIR (fluid-attenuated inversion recovery) sequences (Fig. 2), and ring enhancement on post-gadolinium T1 sequence lesions (Fig. 3), described as multiple brain abscesses. Laboratory tests revealed leukopaenia, thrombocytopaenia, and low percentage of CD4⁺ T-cells 4.9% (normal result 30–55%). The consulted infectologist and hematologist required brain biopsy in order to exclude cerebral lymphoma and multiple metastases. Pathology report showed TE (typical findings commonly referred to as the ‘toxoplasmosis triad’: follicular hyperplasia, the presence of monocytoid cells in subcapsular and trabecular sinuses, and the presence of clusters of epithelioid histiocytes), while her blood samples showed an HIV infection. On the sixth day following admission, the patient was transferred to University Hospital for Infectious Diseases in Zagreb and died 2 days after. Her family then confessed that she had been HIV positive for 10 years and refused any treatment for that infection. The family’s denial of infection as well as ‘hiding information’ concerning the patient’s health from physicians involved in her

treatment caused a delay in proper on-time patient treatment.

Discussion

According to Croatian Public Health Service, there is low incidence of HIV infection and AIDS in Croatia. Between January 1985 and December 2012 there were 1017 HIV-infected cases, out of which 371 developed AIDS and 161 passed away. Average incidence rate of HIV infection in Croatia is 15.0 per million population.¹⁰

There is still a misinformation about HIV among the majority of Croatian population, which presents a great danger for HIV/AIDS transmission.

Toxoplasma gondii is commonly acquired through the ingestion of raw or undercooked meat contaminated with cysts of *T. gondii*, resulting in latent infection. With the onset of immunosuppression, as was the case with our patient, it may preferentially cause a CNS infection resulting in a wide range of clinical presentations.¹¹

The most common clinical manifestations of TE are neurological disorders such as: headache, fever, focal neurological deficits, speech disturbances, cognitive dysfunction, seizures, visual disturbances, and impaired coordination.¹² Thus, TE could mimic other neurological diseases and patients might be hospitalized in the Department of Neurology or Neurosurgery at the hospital, and not the Department of Infectious Diseases as in our case.

As TE is a treatable condition, it is mandatory to make rapid diagnosis and distinguish it from other opportunistic cerebral infections, cerebral lymphoma, multiple metastasis, or multiple brain abscesses. Typical MRI findings suggestive of TE are multifocal parenchymal lesions in basal ganglia, thalamus, corticomedullary junction and cerebellum, hypointense on T1 with hypointense rim, and hyperintense necrotic centre on T2-weighted images with rim or nodular contrast enhancement and 'target' sign, surrounded by vasogenic oedema.^{3,4} Nevertheless, even characteristic lesions are not pathognomonic and in some cases of TE brain MRI revealed T1-hyperintense lesions accompanied by typical multiple high intense lesions on T2-weighted image.⁴

There is incompetence of the serological examination for the immunocompromised patients and around 10% of the patients with TE show no serum anti-toxoplasma antibody response.⁹ Due to the unavailability of this test at our Hospital and Department of neurology, it was not performed upon admission.

The stereotactic brain biopsy ordered and performed at an early stage, during the patient's evaluation, showed a good performance in order to achieve a prompt and accurate diagnosis and to guide the therapeutic scheme in AIDS patients with focal

brain lesions.¹³ Stereotactic brain biopsy was performed following the MRI exam, in order to exclude cerebral lymphoma and multiple metastasis, and to confirm the presence of infection. Following the confirmation of HIV infection and TE, the patient was transferred to University Hospital for Infectious Diseases for definite diagnosis confirmation with positive serum anti-toxoplasma antibody response and further treatment.

Toxoplasmic encephalitis is the most common opportunistic cerebral infection in AIDS patients and, if treated at an early stage, could be highly responsive to antiparasitic chemotherapy.⁷ Its incidence in AIDS patients' ranges from 3 to 40%.^{2,14} If untreated, TE is uniformly fatal.¹⁵ The introduction of HAART has decreased the incidence of AIDS defining diseases¹⁶ and the incidence of toxoplasmosis, but TE can develop in cases where, at admission, there is no information (or it is concealed) about known HIV infection or AIDS and in patients who did not receive any antiretroviral therapy or the antitoxoplasmic prophylaxis, like in our patient.^{1,17,18}

From our experience, we feel there is still a stigma concerning HIV infection and the patient and her family preferred to accept any diagnosis other than the one of AIDS. We believe that if the family had given proper personal history of the patient, mentioning also that the patient was HIV positive for 10 years, the treating physicians would have lost less time in the diagnostic process and accurate diagnosis would have been reached sooner, and by that, the final outcome might have been influenced. However, the patient did not want to accept the possibility of the disease and stopped attending the Infectious Clinic. Moreover, she refused to take any medication for HIV infection, but accepted those for haematological disease, although it was a consequence of the HIV infection. As TE progresses rapidly and is life threatening for AIDS patients, it is recommended to start the antitoxoplasmic therapy promptly when the disease is suspected on the neuroradiology images and laboratory data.⁴

In conclusion, although the diagnosis of TE is difficult and complex because of the lack of pathognomonic MRI or laboratory findings, inadequate data about patient history given by the patient himself, a family member, or caregiver, makes patient compliance a crucial part of obtaining a correct diagnosis in time for treatment. Toxoplasmic encephalitis is a treatable condition, but it is associated with high rates of mortality when misdiagnosed or treated at a later stage. The number of AIDS patients will increase in Croatia and all over the world as well, and the neurologist has to consider TE in sexually active patients with multiple cerebral lesions and without a known prior history of HIV infection. Improvement in

the diagnostic methods and increase in the awareness and knowledge about HIV infection and AIDS is an urgent necessity.

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