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A rare case of an HIV-seronegative patient with *Toxoplasma gondii* meningoencephalitis

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ABSTRACT

Cerebral toxoplasmosis is a common opportunistic infection that causes expansive brain lesions in people living with HIV/AIDS. But it is extremely rarely associated with HIV negative patients. This study presents a case of a 23-year-old male with non HIV-relative cerebral toxoplasmosis. There was an acute onset of the disease. The first symptoms included fever and signs of meningoradicular irritation. Neurological abnormalities progressed in cranial nerves disorders and pyramidal syndrome. The cerebrospinal fluid (CSF) changes were consistent with those of viral meningoencephalitis. CT and MRI showed multiple ring-enhancing lesions with high-intensity signals in cerebrum brain stem and cerebellum. The tests for HIV (ELISA and Western blot) were negative. Serological detection of *Toxoplasma gondii (T. gondii)* IgM and IgG antibodies in the CSF confirmed the diagnosis. Parasitic, bacterial, viral encephalitis and meningoencephalitis, as well as neoplastic metastatic process and other neurological diseases were discussed in the differential diagnosis. The intensity of the disease activity fluctuated during the hospital stay regardless of the adequate therapy.

Background

Toxoplasmosis is an infectious disease caused by an obligate intracellular protozoan parasite called *T. gondii*. A toxoplasma infection usually occurs by one of the following:

- eating raw or undercooked contaminated with bradisoites meat
- ingestion of oocysts through contact with cat feces
- mother-to-child transmission
- organ transplantation and/or by blood transfusion [1,2].

Seroprevalence against *T. gondii* varies significantly in geographical areas from about 11% in the USA to 50–80% in some European, South American and African countries [3].

Severe toxoplasmosis causing damage of the brain is most likely in immunocompromised patients such as individuals with HIV/AIDS. Before introducing the antiretroviral therapy(ART) into the treatment of HIV positive patients 33% of them were reported with toxoplasma encephalitis [1].

In HIV-infected patients the incidence of toxoplasmosis is closely related to CD4 cell count. Clinical manifestation in patients with CD4 + T cell count above 200 cells/L is described rarely. Common symptoms of toxoplasma encephalitis are flu-like symptoms, lymphadenopathy, seizures, hemiparesis, eye and mental disorders [4].

Case presentation

The patient was a 23-year-old man who was living in a village in his private small livestock farm and was an owner of a cat. His past medical history was unremarkable. He presented to the Clinic of Infectious diseases of the University hospital, Stara Zagora with a 3-week history of asthenia, fever - up to 39°C, cough and loose stools, lethargy, confusion, slurred speech and unsteady gait. On admission he complained of a progressively worsening headache, photophobia and dizziness.

The patient was admitted in a generally bad condition, toxic appearing but conscious with a fever –39,6 °C, dry pharyngeal and oral mucoses, whitish coated tongue. There was no skin rash.

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Table 1
Laboratory parameters of cerebrospinal fluid.

Parameters/Data	Leuc. 1–5.10^6/L	Er. 1–5.10^6/L	Sed. Ly (%)	Alb. 0,15-0,45 g/L	Sugar 2,5–3,9 mmol/L	Chloridae 115–132 mmol/L	Pandy
25.04.17	96	32	97	0,66	3,14	115	+
27.04.17	74	86	85	0,51	2,66	123	trace
06.05.17	44	0	70	0,58	2,87	125	–
24.05.17	24	1	Ед.	0,32	3,34	113	–

Cardiovascular and pulmonary exams were unremarkable - heart rate 78 bpm, blood pressure- 110/70 mm Hg, respiratory rate – 22/min and oxygen saturation – 94% on room air. There were enlarged liver –3–3, 5–4 cm and spleen – 1–1,5 cm. The neurological examination revealed:

1. Signs of meningoradicular irritation – severe neck stiffness, positive Brudzinski's neck sign and positive Kernig's sign.
2. VI, central VII and XII cranial nerve lesions on the right side
3. Right hemiparesis
4. Static and locomotor ataxia
5. Brisk tendon reflexes and clonus on the left foot
6. Dysarthria

Laboratory investigations showed anemia, mild leukocytosis with left shift. Renal and liver function tests were unremarkable. There were no hemostatic disorders. There were high levels of C-reactive protein (CRP). CSF changes were consistent with those of viral meningoencephalitis. Table 1**.**

Based on clinical presentation and laboratory findings a provisional diagnosis of serous meningoencephalitis was considered.

Treatment with Ceftriaxone, Amikacin, Mannitol, Dexamethasone, fluids, and multivitamins was started. The patient was treated symptomatically as well. Despite the negative results of pulmonary X-ray and screening tests for tuberculosis (Mantoux test and QuantiFERON®-TB Gold test), tuberculostatic drugs were included in the therapy.

On the first hospital week the patient continued to spike fevers – up to 38 °C (despite of antipyretics). On the 10-th day his condition deteriorated. He had severe headache, bradypsichia, bradylalia, sensory-motor aphasia and III cranial nerve lesion on the right side were demonstrated. On the third hospital week he was clinically improved. The temperature was subfebrile, symptoms of meningoradicular irritation and VI and VII cranial nerve were reduced. Right hemiparesis regressed to monoparesis on the lower limb. On the 21-st hospital day a new febrile peak up to 39,8 °C was registered. The patient appeared anxious and irritable and experienced communication difficulties.

During his hospital stay, the patient underwent several brain imaging tests (CT and MRI) - on the day of admission and thereafter. Figs. 1, 2A, 2B and 3 show some of the most pronounced pathological lesions. Brain CT and MRI images arose a high index of suspicion of a parasitic infection, especially of Toxoplasma infection. A combination of Clindamycin and TMP/SMX was included in the therapy.

Toxoplasma CSF serological tests both IgM and IgG were requested for the patient at the Nacional Reference Laboratory for diagnosis of Parasitic diseases, Sofia. Both tests were positive and this confirmed the diagnosis.

To assess the patient's immune status, 4 classes of immunoglobulins (A, G, M, E) and complement factors (C3, C4) as well as the CD panel parameters were tested. All of them were in the lower reference range. Due to evidence for slight immunological suppression (Table 2) the patient underwent 3 HIV tests with ELISA and 1 with Western blot following nationally validated testing algorithm.

The recommended by Ministry of Health in Republic of Bulgaria laboratory HIV testing algorithm follows these steps: The ELISA test is done first. If the ELISA is positive, a Western blot test is performed. If the ELISA and Western blot test are positive, the viral load must be determined. If ELISA is negative, the Western blot test is performed only in high-risk persons. The testing algorithm is validated by the National Reference Laboratory for HIV/ AIDS in Sofia.

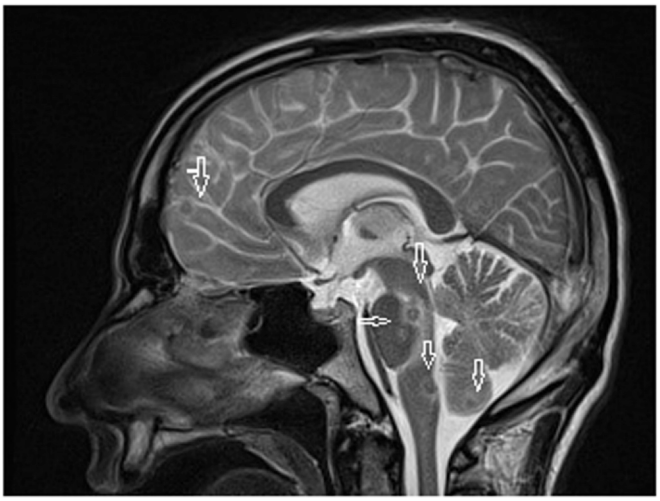

Fig. 1. MRI (27.04) T2 dark fluid sequence, sagittal projection. Presence of ring-line high-signal foci with perifocal polydigital changes as a manifestation of a perifocal edema, situated in the pons, medulla oblongata, cerebellar vermis and frontally in the juxta-cortical region. The presented localization can be associated with pyramidal and motor coordination symptoms.

The our patient HIV testing was as follows:

1. On the day of admission – ELISA negative result.
2. On the 10-th day, when the diagnosis of cerebral toxoplasmosis was confirmed and high index of suspicion for HIV infection arose – ELISA negative, Western blot test negative, too.
3. On the 41-st hospital day – ELISA negative result.

The patient's wife underwent 2 ELISA HIV tests, too. They were all negative.

The patient and his family requested for discharge. He left the clinic with a slight improvement after a 45 hospital stay regardless of a possible risk. The discontinuation of the treatment against medical advice resulted in a lethal outcome.

Discussion

T. gondii is an opportunistic intracellular protozoan parasite that is considered as the most common cause for brain lesions in patients with AIDS [5].

Toxoplasmosis is the leading cause for CNS lesions in patients with AIDS and development of life–threatening encephalitis [6]. Cerebral toxoplasmosis in HIV-negative patients is extremely rare [7]. In immunocompetent adults the infection is usually asymptomatic or cause flu-like symptoms such a fever and discomfort. In immunosuppressed patients *T. gondii* may cause severe CNS infections [8].

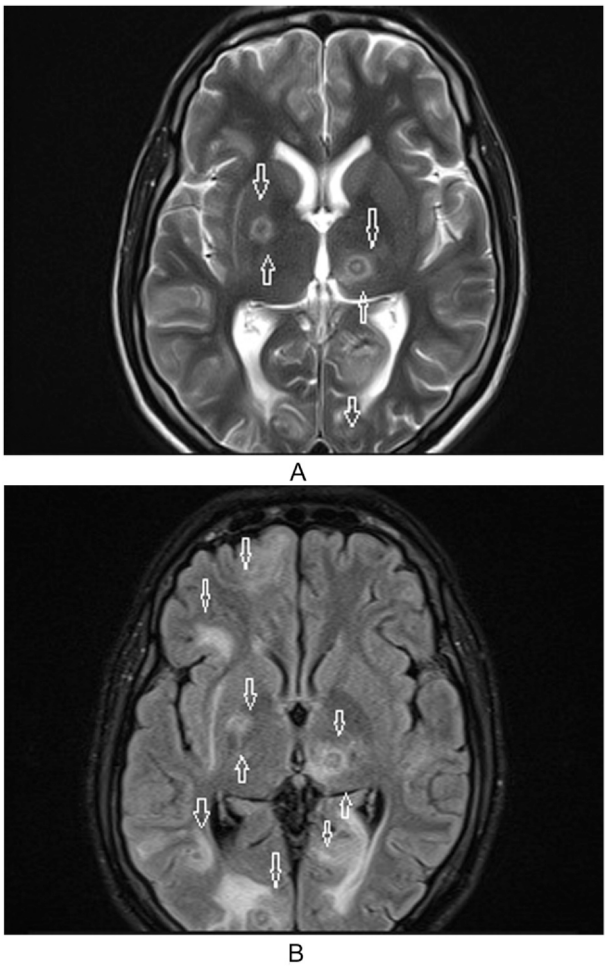

Fig. 2. A. MRI (27.04.) T2 – TSE sequence, axial projection: ring-like high-signal changes are visualized. These are situated asymmetrically from both sides in the basal nuclei. B. MRI (27.04.) T2 dark fluid, axial sequence. The same level is examined with the presented findings which possess the characteristics of a perifocal and periventricular edema. The high-signal changes bilaterally in the periventricular region are more distinct around the posterior horns of the lateral ventricles.

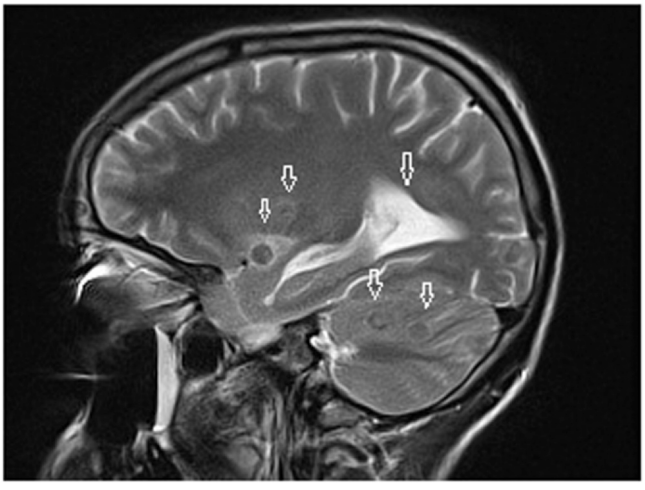

Fig. 3. MRI (16.05) on the T2 weighted sagittal sequence, the fluid is dark. The follow-up MRI shows significant progression of the changes in the meningeal membranes and intra parenchymal in the white brain matter and the periventricular spaces.

Table 2
Markers of CD panel.

CD markers	Value	Reference range
T Lymphs% of Lymphs (CD3+/CD45+)	42	55–84%
T Lymphs% (CD3+)Abs Cnt	520	690–2540.10^6cells/L
T Suppressor% of Lymphs (CD3+CD8+/CD45+)	19	13–41%
T Suppressor Lymphs (CD3+CD8+)Abs Cnt	325	190–1140.10^6cells/L
T Helper% of Lymphs (CD3+CD4+/CD45+)	21	31–60%
T Helper Lymphs (CD3+CD4+) AbsCnt	367	410–1590.10^6cells/L
Lymphocyte (CD45+) Abs Cnt	1229	.10^6cells/L
T Helper/Suppressor Ratio	1,09	0.8–4.2

In this study we present a case of acute meningoencephalitis caused by *T. gondii* in a HIV-negative patient.

In most of the cases the disease develops by reactivation of an earlier, latent infection [9]. According to Carruthers VB et al. one can get infected with *T. gondii* after eating undercooked lamb or pork meat containing parasite's tissue cysts, or drinking water contaminated with *T. gondii* oocysts [10].

In our patient *T. gondii* infection most probably occurred by eating undercooked contaminated with bradisoites pork or ingestion of oocysts through contact with cat feces. The cause of slight immunosuppression in our patient remained unknown. Probably poor sanitation and alcohol abuse were underlying condition that contributed to Toxoplasma infection.

Typically cerebral toxoplasmosis has a subacute onset – 58–89% of the patients. In 15–25% of the cases it can present as an acute disease which manifests with seizures, speech disorders and hemiparesis. Headache is associated with lethargy and altered mental status [11].

The clinical manifestation and course of the disease in the reported case were similar to many other described in the scientific literature. Based on the clinical course, serological CSF tests and MRI findings a diagnosis of cerebral toxoplasmosis was made. The serological tests in our patient showed the simultaneous presence of IgM and IgG antibodies against *T. gondii*. This means that he was experiencing the acute form of the infection. When only IgG antibodies to *T. gondii* were present, the infection probably has been developed over a longer period of time [9].

As it is known cerebral toxoplasmosis in AIDS patients occurs usually when the CD4+T cells count falls below 200.10^6 cells/L and most commonly even below 50.10^6 cells /L [4].

Our patient had slight immune deficiency and his CD4+T cell count was 367.10^6 cells/L.

All of his and his wife's HIV tests were negative.

Diagnosing of the Toxoplasma neuroinfection requires the presence of 3 components: 1. Clinical symptoms corresponding to Toxoplasma infection 2. Specific CNS lesions detected by CT and MRI scans. 3. Positive *T. gondii* serological tests [11]. All these criteria are available in the case described.

In the differential diagnosis, the following possibilities were discussed:

1. Cerebral cysticercosis. Neurocysticercosis is associated with epileptic seizures. Headache, higher levels of irritability, meningeal irritation, cognitive disorders, hemiparesis and palsy are observed. Mononuclear pleocytosis, eosinophils, elevated levels of protein, normal or lower levels of blood sugar are detected in the cerebrospinal fluid. The diagnosis is set on grounds of the ELISA assay which is used for the detection of specific IgM antibodies [12].

   The changes demonstrated by the laboratory test results in our patient were mild proteinorachia and mild pleocytosis with a high prevalence of the lymphocytes and normal glucose levels.

2. Tuberculosis of the CNS. In adult patients, this form of TB is secondary, developing after the primary TB infection located most often in the lungs. The imaging results reveal a large number of small-sized foci situated in the basal region of the brain [13].
   In the case described, the typical X-ray finding is missing. The patient did not respond adequately to the triple tuberculostatic drug therapy. Apart from that, neither the Mantoux test, nor the QuantiFERON TB Gold Test confirmed this diagnosis.
3. Multiple cerebral abscesses. These are associated with various infectious diseases (aspergillosis, cryptococcosis, candidosis), neoplasms and vasculitis.
   The imaging tests reveal a large number of ring-like lesions similar to those described in our case. However, in clinical terms, the brain abscesses are accompanied by constant fever, recurrent seizures, vision disorders, focal neurological deficit, hemiparesis and plegia [14].
   In contrast to this, our patient's fever was remittent and the neurological symptoms were fluctuating.
4. Multiple brain tumor metastases as a result of a primary cryptogeneous malignant process. The brain metastases are the most common intracranial neoplasms in adult patients. 40% of the gliomas and blastomas are demonstrated by similar ring-like lesions [15]. In our case we found no evidence of a primary neoplastic process
5. Multiple sclerosis – demyelinating lesions do not look like a closed ring [16]. In our patient, the clinical criteria for this diagnosis were missing.
6. Cerebral sarcoidosis- rare localization of the disease which occurs with headache, seizures, meningeal irritation, paresthesia, and palsy of cranial nerves III and VII. The brain lesions on the MRI images however, do not possess the typical annular features [17].

Conclusion

Cerebral toxoplasmosis is an opportunistic infection usually occurring in immunocompromised persons especially patients living with HIV/AIDS.

This article presents a case of Toxoplasma infection in a patient without HIV or any history of immunodeficiency. It was difficult to suspect such a diagnose based only on the clinical manifestation on admission.

This case emphasized the need to consider cerebral toxoplasmosis in HIV-negative patient. Early diagnosis and prompt treatment are important in preventing the morbidity and mortality from this cause.

The patient's good adherence is also crucial to the successful treatment.

Ethical Approval

The described case report was approved by the Ethics Committee of the University Hospital, in whose Infectious Diseases Clinic the patient was treated. We have a declaration of consent from the relatives of the described patient to publish the data related to his disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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