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T. A. DOVBONOS

O. O. Bogomolets National Medical University, Kyiv

Tuberculosis meningitis in HIV positive patient. A case report and literature review

Tuberculosis of central nervous system (CNS) is one of the most devastating forms of micobacterial infection with high mortality. Basal meningitis accounts for about 70% of CNS tuberculosis and about 1/3 of cases have atypical manifestations. The risk of acquiring neurotuberculosis in HIV patients is 10 times higher than in non-HIV individuals and its related mortality exceeds 50%. In the article the case of tuberculosis meningitis in HIV positive patient with hyperkinetic hemiballism manifestation is presented. We reviewed literature on pathogenesis of motor disorders, update diagnostic criteria and treatment approaches of the co-infection.

Key words: tuberculosis meningitis, hemiballism, HIV-infection.

Involvement of the central nervous system (CNS) is known as the most devastating manifestation of tuberculosis (TB) with high mortality [3, 5, 22, 26]. Neurotuberculosis usually caused by reactivation of latent infection has been reported in approximately 5—15% of all extrapulmonary TB cases. While TB meningitis is the most common form of childhood and accounts for about 70% of CNS tuberculosis, tuberculomas and spinal tuberculosis are invariably an adult manifestation [9, 10].

Patients with TB meningitis develop typical meningial symptoms including headache, fever, and stiff neck, although these signs may be absent in the early stages. The duration of symptoms before presentation ranges from several days to several months. Cranial nerve impairment (most commonly III, VI, and VII), hemiparesis, paraparesis, and seizures are common and should raise the possibility of neurotuberculosis. About 1/3 of TB meningitis patients had different atypical manifestations [4, 9].

A diagnosis of suspicious TB of CNS should trigger a search for concomitant pulmonary disease, which has implications for infectivity. An extraneural focus of tuberculosis should be sought clinically and radiologically as it may indicate safer and more accessible sites for diagnostic samplings. Chest X-ray is suggestive of active or previous pulmonary TB in approximately 50% of cases. Cerebrospinal fluid (CSF) should be sent for routine analyses (cell counts and differential, protein level, glucose level) and microbiologic tests for bacteria, fungi, and micobacterii tuberculosis. Pleocytosis with lymphocytic predominance, high protein levels, and low glucose levels are the hallmark findings in the CSF of patients with TB meningitis. [5]. Treatment of neuroturbeculosis is generally with standard quadruple therapy for 9—12 months. Knowledge of the penetration across the blood-brain barrier of the various antituberculosis agents used in central nervous system TB treatment is important. All patients with TB meningitis may receive adjunctive corticosteroids at presentation regardless of disease severity even for those with HIV infection. Early ventriculo-peritoneal shunting should be considered in those with hydrocephalus failing medical management [3, 10, 25, 26].

Diagnosis of TB meningitis is considered definitive, if *M. tuberculosis* is found in CSF by CSF smearing and culture or TB-PCR. According to the definition of suspicious TB meningitis, the characteristics of tuberculous CSF should be found (white blood cells

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Довбонос Тетяна Анатоліївна, к. мед. н., доцент кафедри неврології
E-mail: tetanatdovbonos@ukr.net

> $10 \cdot 10^6$/L [mainly lymphocytes]; protein > 40 mg/dL; reduced ratio of CSF glucose to serum glucose [< 0.6 mg/dL or < 60 mg/dL]), and at least one of following findings was present: (1) hematogenous disseminated pulmonary tuberculosis: tubercle bacillus was separated from other tissues except for CSF, or active pulmonary tuberculosis was present; (2) Imaging findings: cerebral CT or MRI showed characteristics of TB meningitis; (3) history of past illness: tuberculosis infection or exposure to TB; (4) Diagnostic therapy: symptoms improved significantly after anti-TB therapy [9, 16].

The severity of TB meningitis may be determined according to the TB meningitis grading system: grade I equivalent to Glasgow Coma Scale (GCS) 15, indicating no focal nervous system signs; grade II equivalent to GCS 15, accompanied by nervous dysfunction, or GSC 11—14; grade III equivalent to GCS ≤ 10 [1, 9]. H. Kaur et al. showed with multivariate regression analysis that mortality was the highest in confirmed cases of the stage III TB meningitis [11].

TB menigitis is seen increasingly in patients with immunosupression or HIV [7, 17]. The risk of acquiring neurotuberculosis in HIV patients is 10 times higher than in non-HIV individuals and its related mortality exceeds 50 %. From this view, an HIV test is recommended with any TB diagnosis. Both multidrug-resistant and extensively drug-resistant tuberculosis can spread rapidly among an immunocompromised population, with resulting high mortality rates. Movement disorders could be a neurological complication of acquired immune deficiency syndrome and sometimes represent the initial manifestation of HIV infection. Patients with HIV and movement disorders usually present with clinical features such as peripheral neuropathy, seizures, myelopathy and dementia. Other movement disorders diagnosed in HIV positive patients include torsial dystonia, hemiballism, chorea, myoclonus, tics, paroxysmal dyskinesias and Parkinsonism [2, 19]. Some motor dysfunctions seen in the setting of global cognitive and behavioral abnormalities has been termed the AIDS dementia complex, but approximately 50 % of those individuals dying from HAD will have HIV encephalitis [24].

According to some scientists antiretroviral therapy and antituberculosis treatment in HIV positive patients should be initiated at the same time, regardless of CD4 cell counts [7, 13]. Some other current guidelines recommend starting antiretroviral treatment within a few weeks of antituberculosis therapy for patients with CD4 cell counts < 350 cells/μL. Challenges include pill burden and patient compliance, drug interactions, overlapping toxic effects, and immune reconstitution syndrome. So important questions about the drug regimens and timing of antiretroviral therapy remain and ongoing trials may answer many of these unresolved questions [23].

T. Raut et al. reported that hydrocephalus occurred in approximately two-third of patients with tuberculous meningitis and had an unfavorable impact on the prognosis [18]. Other predictors of unfavorable outcome include age > 40 years, past history of tuberculosis, presence of basal exudates, change in consciousness, and focal neurological signs [9, 13].

A case report

We present a case of a 67-year-old female patient with arterial hypertention who was brought to the emergency room due to abnormal posture of her right arm and memory disorders. The duration of symptoms was several days before presentation, but general weakness and loss of weight were mentioned earlier. There was history of past tuberculosis illness in childhood. Family medical history was unremarkable. In neurological status mild intelligence reduction with somewhat disorientation to time and place, ataxia and hemibalism in right upper limb with hypotonia in it were found out. The involuntary arrhythmic movements of a forcible, rapid, jerky type and of a wide range and a flinging nature most commonly involved the proximal parts of the right arm. There were no headache, stiff neck and other typical symptoms of meningitis as well as signs of cranial nerves involvement. Muscle strength and sensation were preserved.

Essential clinical investigations as well as urgent cranial CT and chest X-ray were required. Cerebral CT scan revealed multiple hypodensive lesions mostly subcortically in both hemispheres (Fig. 1).

A chest X-ray revealed the signs of upper lobular left-side pneumonia. Chest CT was also done in search of lung lesions suspicious of TB and disseminated pulmonary lesions were seen (Fig. 2).

The patient had CSF taken, and the following tests performed: total cell count, cytological classification, detection of glucose, proteins. The patient had increased CSF pressure, total count — 21 cells (80 % lymphocytes), normal protein level (0.33 g/L) and reductions in glucose (1.3 mmol/L). Ziehl-Neelsen stain, and polymerase chain reaction for *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* were negative. Culture results for tuberculosis were not yet available. The patient was also found HIV positive (Alene, Profitest).

Diagnosis of TB meningitis was presumed as the patient had clinical, biochemical and radiological features of suspicious TB. Antimycobacterial treatment with isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide was started with adjunctive dexametasonum administration. However, the patient remained neurologically severely impaired and after 10 days she died. Pathomorphologicaly miliary lung tuberculosis and TB meningitis were verified.

So the case of severe disseminated infection with central nervous system involvement due to a mycobacterium described here occurred in a profoundly immunosupressed patient and hemiballism was associated with a lesion in the subcortical region. Hy-

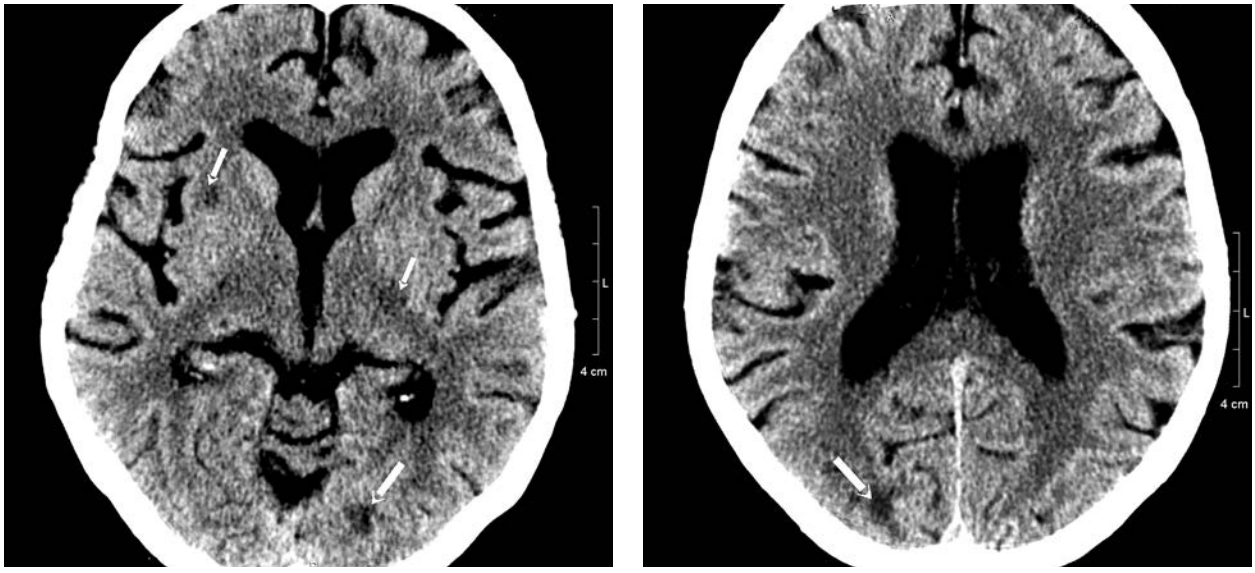

Fig. 1. *Cerebral CT scan with bilateral subcortical hypodensive lesions (arrows)*

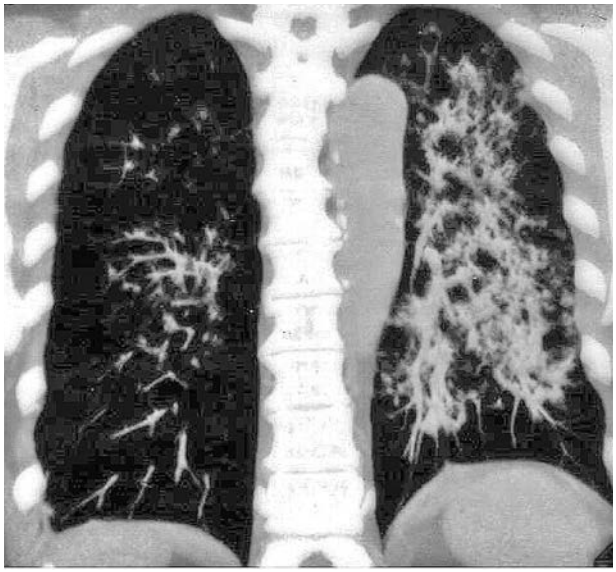

Fig. 2. *Disseminated pulmonary tuberculosis on chest CT*

podensive subcortical lesions could be signs of encephalopathy of TB and/or AIDS genesis. The direct infection of the basal ganglia by *M. tuberculosis* and HIV is also suspected.

The precise mechanisms of these disorders aren't investigated well, but there is substantial evidence from neuroradiologic and pathological studies supporting dysfunction of the basal ganglia. Positron emission tomography studies have shown relative hypermetabolism in the basal ganglia and thalamus in the early stages of HIV dementia, with global cerebral hypometabolism noted in more advanced stages [20]. Approximately 50 % of patients with HAD demonstrate a microglial nodule encephalitis with multinucleated giant cells, with prominent involvement of the putamen and caudate nuclei. Opportunistic diseases in HIV may also demonstrate a predilection for the basal ganglia. In patients with AIDS, hemichorea–hemiballism is the most frequently associated with Toxoplasma abscesses [19, 27].

In 1986 the HIV patient with hemichorea–hemiballism was presented [14], and in a year three other cases were described [15]. Since then, a growing number of patients with HIV-related ballism have been reported. The hyperkineses typically were only one body side with acute or subacute clinical onset as a result of multiple cerebral lesions (rather than a single one). The cerebral structures more commonly affected are the subthalamic nucleus, thalamus, head of the caudate, putamen, globus pallidus, midbrain and internal capsule. Ballism or chorea were shown to be convincingly associated with subthalamic nucleus damage or its efferent pathways, which removes excitation of the globus pallidus, thus disinhibiting the ventrolateral and ventroanterior thalamic nuclei receiving pallidal projections [12]. Potential neurotoxins include HIV proteins (gp120, tat) and substances produced by macrophages (glutamate, cytokines, nitric oxide, quinolinic acid).

On the other hand hyperkinesis were presented in HIV negative patients with neurotuberculosis [6]. A rarer form of CNS TB, tuberculous (allergic) encephalopathy, as a result of delayed hypersensitivity reaction towards tuberculoprotein was described in vulnerable populations with a preceding or concurrent tuberculous infection. Some authors suspect microglial-oligodendrocyte interactions to be worth further studies to broaden the understanding of initiating and attenuating the CNS immune responses [21]. It is known that *M. tuberculosis* activate monocytes release factors into the local microenvironment that rapidly stimulate microglia to produce matrix metalloproteinase (MMP-1 and MMP-3) and induce tissue damage through degradation of various matrix-associated proteins. Microglia are known to demonstrate cytotoxic behav-

ior towards oligodendrocytes via a NO-dependent mechanism requiring membrane-bound tumor necrosis factor-α and a local spike in extracellular glutamate and excitotoxic cellular death [8].

Conclusions

Although the onset of TB meningitis in HIV positive patient is insidious and as a rule it has non-specific manifestations, resulting in diagnostic difficulties, hemibalism may be a variant of the clinical symptoms. Data of brain CT may be not enough to prove CNS involvement so very patient with suspicious TB meningitis should be evaluated by imaging with contrast enhanced CT or MRI. HIV test is preferable with any TB diagnosis. Chest CT is recommended for patients with suspicious TB meningitis because concomitant hematogenous disseminated tuberculosis may be undiagnosed by routine chest X-ray. Further researches into the epidemiology, immune mechanisms, diagnosis, treatment, and prevention of TB meningitis in HIV positive persons are urgently needed.

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Т. А. ДОВБОНОС
Національний медичний університет ім. О. О. Богомольця, Київ

Туберкульозний менінгіт на тлі ВІЛ-інфекції. Опис клінічного випадку та огляд літератури

Туберкульоз центральної нервової системи належить до найтяжчих форм мікобактеріальної інфекції за показниками летальності. Частка базального менінгіту становить близько 70 % від усіх випадків туберкульозу нервової системи. В третині випадків він супроводжується появою атипової симптоматики. У ВІЛ-інфікованих пацієнтів ризик захворюваності на нейротуберкульоз збільшується у 10 разів, а летальності — на 50 %. Описано випадок туберкульозного менінгіту на тлі ВІЛ-інфекції, який маніфестував у вигляді гіперкінетичних порушень за типом гемібалізму. Наведено сучасні дані щодо патогенезу рухових порушень, діагностичних критеріїв і лікувальних підходів у разі зазначеної ко-інфекції.

Ключові слова: туберкульозний менінгіт, гемібалізм, ВІЛ-інфекція.

Т. А. ДОВБОНОС
Национальный медицинский университет им. А. А. Богомольца, Киев

Туберкулезный менингит на фоне ВИЧ-инфекции. Описание клинического случая и обзор литературы

Туберкулез центральной нервной системы относится к наиболее тяжелым формам микобактериальной инфекции по показателям летальности. Доля базального менингита составляет около 70 % от всех случаев туберкулеза нервной системы. В трети случаев он сопровождается появлением атипичной симптоматики. У ВИЧ-инфицированных пациентов риск заболеваемости нейротуберкулезом увеличивается в 10 раз, а летальности — на 50 %. Описан случай туберкулезного менингита на фоне ВИЧ-инфекции, который манифестировал в виде гиперкинетических нарушений по типу гемибализма. Приведены современные данные о патогенезе двигательных нарушений, диагностических критериях и лечебных подходах в случае упомянутой ко-инфекции.

Ключевые слова: туберкулезный менингит, гемибаллизм, ВИЧ-инфекция.

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