

Pathomorphological peculiarities of tuberculous meningoencephalitis associated with HIV infection

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Abstract: *Background and aims:* One of the most severe manifestation displays of tuberculosis (TB) generalization is meningitis/meningoencephalitis. The purpose of this work was to improve the diagnostic efficiency of TB central nervous system (CNS) affection in human immunodeficiency virus (HIV)-infected persons. *Materials and methods:* Meninges and cerebral tissues, taken from died patients, who were HIV-infected and dead from TB of CNS affection, were investigated histologically. *Results and discussion:* Our examination showed that clinical course of the pathologic process loses the peculiarity of TB-undulating character, and changes in tissues have monomorphism that appears in the presence of the same type of granulomas with a few Pirogov–Langhans cells. Alterative reactions with formation of the large fields of caseous necrosis, necrotic foci, areas of infiltration with polymorphic cellular elements went out on the first plan in the disorder of cerebrum in patients with the terminal stage of HIV infection. The tendency to decrease in inflammatory–proliferative processes was observed, which is confirmed by the presence of the poorly expressed cellular reaction on the peripheries of foci of caseous necrosis. *Conclusion:* Morphologic features of tuberculous meningoencephalitis in HIV-infected patients are the presence of edema, gliosis, thrombovasculitis, small focal hemorrhage, tuberculous granuloma formation with a small number of Pirogov–Langhans cells, and the prevalence of alterative–exudative reactions.

Keywords: brain, tuberculosis, HIV infection, histology, meningoencephalitis

Introduction

The increasing global burden of tuberculosis (TB) is linked to human immunodeficiency virus (HIV) infection [1]. TB is the most common opportunistic infection in HIV-infected persons. Immunosuppression due to HIV infection promotes the risk of infection by *Mycobacterium tuberculosis*, complicates clinical displays, diagnostics, and treatment of the disease; and forces the doctor differentiate TB and other opportunistic infections [2]. According to WHO data, among patients infected with HIV, TB occurs in about 30% of patients and causes approximately 25% of deaths due to AIDS worldwide [3, 4].

TB involving the central nervous system (CNS) causes considerable morbidity and mortality and it is rarely observed in non-immuno-compromised hosts [5]. CNS involvement, one of the most devastating clinical manifestations of TB, is noted in 5–10% of extrapulmonary

TB cases, and accounts for approximately 1% of all TB cases [6]. HIV-infected patients have a high incidence of tuberculous meningitis as well [7]. One of the most severe manifestation displays of TB generalization is meningitis/meningoencephalitis, which is characterized by the extremely high indices of lethality [8]. The exact incidence and prevalence of tuberculous meningitis in HIV-infected patients are not known [7, 9].

In connection with the above, the purpose of this work was to improve the diagnostic efficiency of TB CNS affection in HIV-infected persons based on the complex of clinical laboratory and morphologic investigations.

Materials and Methods

Material was collected from Kharkiv Regional Infectious Hospital under our supervision in a period from

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2008 to 2013. Routine laboratory studies, biochemical tests, immunological (immunofluorescence assay), molecular genetics (polymerase chain reaction), bacteriological [inoculation of cerebrospinal fluid (CSF) on the Lowenstein–Jensen medium], radiometric (BACTEC), bacterioscopy (Romanovsky–Giemsa CSF staining), pathomorphological [hematoxylin and eosin (H&E) and Nissl staining], instrumental [computer tomography (CT) and/or magnetic resonance tomography (MRT)], and statistical methods were performed.

Bacteriological method

Planting material on Lowenstein–Jensen medium is carried out in the bacteriological laboratory. The growth of the first colonies is noted after 4–8 weeks.

Radiometric (BACTEC) method

A fluorescent compound is embedded in silicone on the bottom of 16 × 100 mm round bottom tubes. The fluorescent compound is sensitive to the presence of oxygen dissolved in the broth. Initially, the large amount of dissolved oxygen quenches emissions from the compound and little fluorescence can be detected. Later, actively respiring microorganisms consume the oxygen and allow the fluorescence to be detected.

Tubes are filled with samples in the broth and continuously incubated at 37 °C. The tubes are monitored for increasing fluorescence to determine whether the tube is instrument positive, that is, the test sample contains viable organisms. Fluorescence can be recorded by automated instruments such as Becton Dickinson's BACTEC MGIT 960 System, or manually using Wood's lamp or other long-wave UV light source.

Bacterioscopy (Romanovsky–Giemsa CSF staining)

A thin film of the specimen on a microscope slide is fixed in pure methanol for 30 s, by immersing it or by putting a few drops of methanol on the slide. The slide is immersed in a freshly prepared 5% Giemsa stain solution for 20–30 min (in emergencies 5–10 min in 10% solution can be used), then flushed with tap water and left to dry.

Meninges and cerebral tissues, taken from the frontal cortex, temporal lobe (including hippocampus), basal ganglia, and thalamic region of eight patients (five males and three females) on autopsy which were HIV-infected and dead from *M. tuberculosis* CNS affection at age (38.0 ± 1.3 years) with the development of meningoencephalitis. Comparison groups had been formed with person died of tuberculous meningoencephalitis without HIV

infection and in accident. Same materials, age, and gender had been applied in comparison groups. The material was fixed in 10% neutral buffered formalin and then subjected to standard proceeding and embedded in paraffin. Serial sections had been prepared from the blocks with thick 5×10^{-6} m. Slides were stained with H&E and Nissl methods.

The procedure was strictly done in compliance with the Declaration of Helsinki after approval from the Regional Ethical Review Board at Kharkiv National Medical University, protocol 3, 2015.

Results

Under our supervision in Kharkiv Regional Infectious Hospital in a period from 2008 to 2013, there were 475 HIV-infected persons on the different stages of illness. Of which 90 (18.9%) patients died of AIDS. The clinical picture of CNS affection was observed in 197 (41.5%) persons and etiology was diagnosed only in 116 (58.9%) patients. CNS affection caused by *M. tuberculosis* was detected in 32 (27.6%) cases. Males were ill in 3.6 times more frequently with TB – 25 (78%) and 7 (22%), respectively. Middle age was 34.8 ± 0.9 years.

Duration from a moment of HIV infection identification up to the first displays of TB CNS affection was 2.8 ± 0.7 . The disease began gradually to improve. Patients were hospitalized on 53.0 ± 8.2 day of disease in moderate condition 18 (56%) persons and in severe 10 (31%).

Severity of the disease was determined not only by intoxication and neurologic syndromes, but also by formation of such severe complication as cerebral edema, which was the direct reason of patient's death. Lethality was 59.4%. CNS affection caused by *M. tuberculosis*, progress more frequently as meningitis or meningoencephalitis – 26 (81%) and encephalitis – 6 (19%) patients.

There were complains on general weakness at 28 (87.5%) patients. Headache that was more frequently diffuse and increased in evening time marked 28 (87.5%) patients with TB meningitis or meningoencephalitis. The headache was intensive and accompanied by nausea in 12 (37.5%) cases, by vomiting in 14 (43.8%). Dizziness registered in 14 (43.8%) cases. Fever was subfebrile (59.4%) and febrile (34.4%). Anorexia was marked in 10 (31.3%) patients.

On the physical examination, disturbances in orientation in place, in time, and in relation to personality were determined in 10 (31.3%) patients. Meningeal signs were expressive. They were characterized by neck stiffness in 29 (90.6%) cases, Brudzinski's sign in 4 (12.5%) patients, and Kernig's sign in 29 (90.6%) patients. Motor disturbances (hemiparesis, paraparesis, and tetraparesis) were determined in 10 (31.3%) cases. Pathological reflexes appeared in 5 (15.6%) patients: Babinski sign was positive in 3 (9.4%) and Oppenheim sign in 2 (6.2%) patients.

Appearance of the symptoms of pyramid tract defeat testified the severity of affection of cerebrum separate departments as the consequence of edema changes distribution in the brain tissue. Bulbar palsy syndrome was observed in 2 (6.2%) patients.

In clinical blood test of HIV-infected patients with *M. tuberculosis*, CNS affection was found to diminish the general amount of leucocytes and erythrocytes (with reduction of hemoglobin), increase in erythrocyte sedimentation rate, lymphocytopenia, and high absolute neutrophil count. Lymphocyto-neutrophilic pleocytosis, elevation of protein level, decline of glucose, and chlorides concentration were educed at CSF. The disease progressed in the background of deep immunodeficiency. The average value of CD4+ cells was 90.9 ± 17.4 cells/ μ l.

At macroscopic examination of brain autopsy of HIV-infected with *M. tuberculosis*, it was educed in development of meningoencephalitis that the most frequent localization of tubercular injury was basilar departments. During the dissection, in all cases, the dura mater was tensed and did not pleat. Pia was very edematous and picture of gyri was flattened. Dense muddy mass had been revealed on the base of the brain in the region of the pons, medulla oblongata, and the medial surface of the hemispheres of the cerebellum under pia in four cases. Porridge-like areas of grayish–yellowish color with brownish-cherry centers had been identified in three cases, whereas in two cases, these areas had been localized in the area of the medial surface of the hemispheres. The

cut surface of the cerebral hemispheres was sharply swollen in all cases. In three cases, the presence of flabby colorful dirty grayish–yellowish foci measures from 1×1 cm to $2 \times 2 \times 2$ cm was noted; such sites are often localized in the cortex of the temporal–parietal region and in the basal ganglia of the parietal part.

The lateral ventricle lumens were expanded in all cases, contain clear fluid, ependyma of lateral ventricle was smooth. In one case in the lower-side wall of the right ventricle in the area 1×1.5 cm structure was disturbed, ependyma was loose and porous. In all cases, the vessels were thin-walled and unevenly congested.

Inflammatory-infiltrative and necrotic lesions (*Fig. 1*) have been revealed in the brain of deceased HIV-infected patients with TB with the presence of acid-fast bacilli, foci of caseous necrosis, exudation, and alteration. Histological examination of meninges revealed the domination of granuloma formation with areas of centrally located caseous necrosis, thrombovasculitis, and fibrinopurulent exudate.

Focal gliosis (*Fig. 2*) of white matter has been predominantly detected in the frontal lobes with demyelination. The marked perivascular and pericellular edema with extensive areas of cytoplasmic vacuolation, presence of perivascular optical cavities or areas with signs of karyolysis, and destruction of brain substance with glial reaction in cerebral tissue have been revealed in all cases. Accumulation of lipofuscin has been identified in the bodies of neurons (*Fig. 1*) and choroid plexus epithelium in each case.

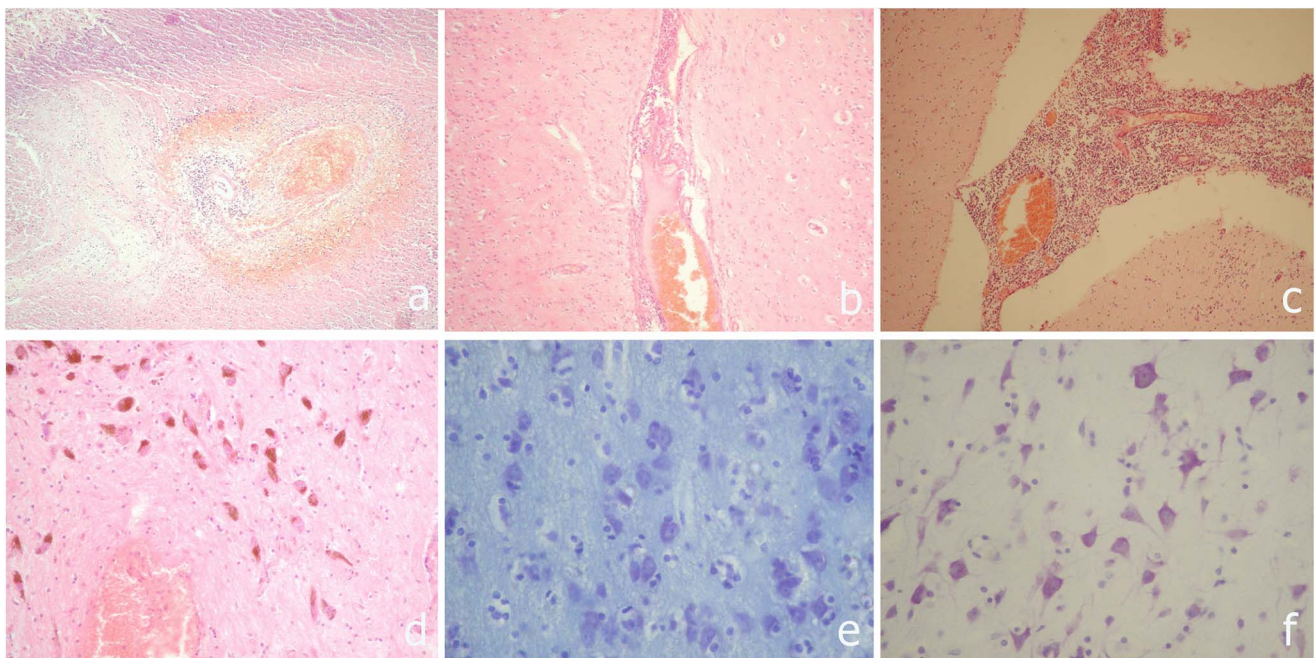


Fig. 1. Inflammatory–infiltrative and necrotic changes surround vessels with perivascularitis (a, H&E staining, 100 \times); vasculitis with thrombus formation and degenerative process in surrounding cerebral tissue (b, H&E staining, 100 \times); development of fibrinopurulent meningitis (c, H&E staining, 100 \times); accumulation of lipofuscin in the bodies of neurons (d, H&E staining, 200 \times); uneven glial neuron distribution and reducing axons with presence of pericellular edema (e and f, Nissl staining, 400 \times)

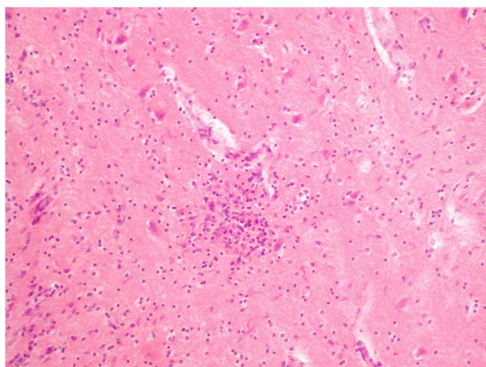


Fig. 2. Perivascular focus of gliosis in the presence of inflammatory cells (H&E staining, 200×)

It should be noted that the specific cellular responses as the formation of granulomas with epithelioid and giant Pirogov–Langhans cells are missed or have not expressed character; the plasmatic and reticular cells predominated in reduced granulomas, whereas lymphocytes and macrophages were at single amounts.

On comparing the morphological patterns and the duration of immunodeficiency, the inhibition of granuloma formation at least during the immune deficiency is detected.

The small arteries and capillary channel of microcirculatory bed are characterized by swelling of the endothelium till the appearance of vacuoles. The basement membrane is thickened, friable with foci of granular disintegration. There is an accumulation of cellular elements of the lymphoid type around the capillaries. The basal membrane of capillaries and small blood vessels (arterioles and venules) with uneven thickness and presence of foci of basement membrane disappearance.

In addition, there are marked inflammatory–proliferative and productive changes with the presence of luminal narrowing of cerebral vessels with areas of cerebral infarction surround vessels with significant changes. Perivasculitis, consisting of acute and chronic inflammatory cells, has been revealed in all cases and it sometimes included multinucleated cells.

Astrocytes surrounding vessels of microcirculatory bed are injured with degenerative changes till necrobiosis. Amount of astrocytes surround microvascular vessels is slightly higher than number of cells from different individuals of the same age without a combination of HIV and TB [2–6 cells around the vessels of superficial cortical layers and 1–3 cells in the deep layers of the cortex and the white matter (normally 1–5 and 3–5, respectively)]. Sizes of astrocytes are characterized with some enlargement of astrocytes body. Cells' shape is from rounded to polygonal. There are Nissl substance grains in astrocytes around the nuclei with different grain sizes. Such granularity is not defined in healthy individuals of the same age.

Processus of cellular elements are numerous, partly smooth, and partly branched. In addition, often the presence of astrocytes can be detected only by the presence of processus, as only the accumulation of granules of different sizes is determined on the ground of their bodies. Astrocytes are not determined around some blood vessels, as opposed to control.

Perivascular hemorrhage zones have been revealed with size from microscopic to large areas in addition to areas of necrosis associated with cerebral ischemic injury.

Tuberculous meningoencephalitis has been characterized by localization of the most pronounced changes in the basilar parts. In addition, histological examination of the meninges revealed fibrinous-purulent depositions with swelling of the meninges, congestion of blood vessels, massive serous, purulent, or serous–purulent inflammation. There are signs of edema, gliosis, thrombovasculitis, small focal hemorrhage, tuberculous granuloma formation with a small amount of Pirogov–Langhans cells or their lack, and the prevalence of alternative–exudative reactions. Signs of septic replacement mass by connective tissue have been revealed in three patients.

Discussion

The proportion of new extrapulmonary TB cases has increased [10, 11]. Our results showed that mortality of adult patients hospitalized with TB had remained substantial in settings with HIV prevalence and CNS involvement.

The spectrum of meningitis in HIV-affected communities can be expected to change toward a predominance of tuberculous meningitis from one side and level for 55%–70% HIV-positive in tuberculous meningitis patient from other side. Diagnosis was often difficult, leading to treatment delay or even omission [12–14]. Many prognostic factors for CNS have been reported, including age, disease stage, level of consciousness, the presence of extra-CNS TB, the isolation of *M. tuberculosis* from CSF and its biochemical studies, hydrocephalus, and infarction [9, 15]. Nonetheless, the mechanisms that lead to brain structural and functional abnormalities and that mediate cognitive and behavioral outcomes remain unclear. One of the major difficulties encountered in clinical practice is distinguishing meningitis/meningoencephalitis from other subacute meningoencephalitides in HIV-infected patients [7, 16–19].

Our examination showed that clinical course of the pathological process loses the peculiarity of TB undulating character, and changes in tissues have monomorphism that appears in a presence of the same type of granulomas with a few Pirogov–Langhans cells. Alternative reactions with formation of the large fields of caseous necrosis, necrotic supportive focuses, areas of infiltration

with polymorphic cellular elements went out on the first plan in the defeat of cerebrum in patients at the terminal stage of HIV infection. Except for the widespread foci of caseous necrosis with a poorly expressive cellular layer, the multiple areas of the purulent melting of tissues were educed in the brain of patients that died of TB and HIV co-infection.

For the pathomorphological features of tuberculous meningitis/meningoencephalitis on a background of HIV-induced immunodeficiency, there were also characteristic features such as inflammatory and proliferative-productive changes in the walls of cerebral vessels that resulted in their narrowing and quite often – in the development of inferior tissues infarctions. Such areas of ischemia are determined on CT or MRT of brain and can become a basis for misdiagnosis of strokes of different genesis.

To summarize, in the tissue of cerebrum at HIV-infected patients, the tendency of decreasing in inflammatory–proliferative processes was observed, which is confirmed by the presence of the poorly expressed cellular reaction on the peripheries of focuses of caseous necrosis and absence (or presence of only a few) of typical tubercular granulomas. There is a tendency that the more severe is the stage of immunodeficiency, the productive reactions are less expressed. Morphological displays of *M. tuberculosis* lesions of CNS in HIV-infected persons characterized by predominance of alterative–exudative reactions, which showed up both forming of typical tuberculous granulomas with the centrally located areas of caseous necrosis in majority of them and presence in the tissues of areas of the caseous masses with the poorly expressed peripheral cellular reaction.

Conclusion

In HIV-infected patients with morphological features of tuberculous meningoencephalitis localization of the most pronounced changes is observed in the basilar parts with the presence of edema, gliosis, trombovasculitis, small focal hemorrhage, tuberculous granuloma formation with a small number of Pirogov–Langhans cells, and the prevalence of alterative–exudative reactions.

TB of the brain that develops in patients with HIV infection is characterized by some features of anamnesis, clinical and radiographic and laboratory manifestations, which significantly complicates timely diagnosis of the disease and demonstrates the necessity for additional diagnostic criteria for this type of comorbidity.

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Authors' contribution: VMK: manage investigation, literature review; AVB and AVG: clinical investigation of patients with description

performing laboratory tests, data analysis; OSS: selection of patients, data analysis; VVG: performing morphological investigation.

Conflict of interest: The authors declare no conflict of interest.

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