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CLINICAL AND MORPHOLOGICAL ANALYSIS OF A FATAL CASE OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

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Progressive multifocal leukoencephalopathy is a rare severe progressive demyelinating disease of the central nervous system that occurs as a result of reactivation of polyomavirus in immunodeficiency states. Currently, progressive multifocal leukoencephalopathy is an incurable disease with unfavorable outcomes. The article analyzes a case of progressive multifocal leukoencephalopathy based on the medical history and pathological examination of the deceased. In this case, the patient had no signs of immunosuppression and the diagnosis was confirmed histologically. Some publications indicate that progressive multifocal leukoencephalopathy without overt immunosuppression may account for a significant proportion of cases of this disease, and the frequency of progressive multifocal leukoencephalopathy without overt immunosuppression may potentially be even higher. It can be assumed that a period of dysfunction in the immune surveillance of the viral life cycle may be sufficient to allow the necessary viremia to occur in immunocompetent patients. Although progressive multifocal leukoencephalopathy is rare, doctors should always keep in mind the possibility of developing this disease with a similar clinical picture in patients without signs of immunosuppression.

Key words: pathomorphology, JC-virus, diagnosis, etiology, immunodeficiency.

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КЛІНІКО-МОРФОЛОГІЧНИЙ АНАЛІЗ ЛЕТАЛЬНОГО ВИПАДКУ ПРОГРЕСУЮЧОЇ МУЛЬТИФОКАЛЬНОЇ ЛЕЙКОЕНЦЕФАЛОПАТІЇ

Прогресуюча мультифокальна лейкоенцефалопатія – рідкісне тяжке прогресуюче демієлінізуюче захворювання центральної нервової системи, що виникає внаслідок реактивації поліомавірусу при імунодефіцитних станах. Наразі прогресуюча мультифокальна лейкоенцефалопатія є невиліковним захворюванням з несприятливими наслідками. У статті проаналізовано випадок прогресуючої мультифокальної лейкоенцефалопатії на основі історії хвороби та патологоанатомічного дослідження померлого. При цьому у пацієнта не було ознак імуносупресії, діагноз був підтверджений гістологічно. Деякі публікації вказують на те, що прогресуюча мультифокальна лейкоенцефалопатія без явної імуносупресії може становити значну частку випадків цього захворювання, а частота прогресуючої мультифокальної лейкоенцефалопатії без явної імуносупресії потенційно може бути ще вищою. Можна припустити, що період дисфункції імунного нагляду за життєвим циклом вірусу може бути достатнім для виникнення необхідної віремії в імунокомпетентних пацієнтів. Хоча прогресуюча мультифокальна лейкоенцефалопатія зустрічається рідко, лікарі завжди повинні пам'ятати про можливість розвитку цього захворювання з подібною клінічною картиною у пацієнтів без ознак імуносупресії.

Ключові слова: патоморфологія, JC-вірус, діагностика, етіологія, імунодефіцит.

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At present, the study of the ways of infection, pathogenesis, clinical course, morphological changes in various infectious diseases are a vitally important issue in medical and social sphere [3].

Progressive multifocal leukoencephalopathy (PML) is a rare severe progressive demyelinating disease of the central nervous system that occurs as a result of reactivation of polyomavirus (JC virus) in immunodeficiency states, which has an unpredictable course with often fatal outcome and no effective treatment [2].

It is believed that PML is essentially an opportunistic viral infection caused by the JC virus (the name comes from the first letters of the name and surname of the patient John Cunningham, who was first diagnosed with this pathogen). It is a DNA double-stranded ring virus from the polyomavirus family. The virus capsid contains three viral proteins: VP1, VP2 and VP3. The predominant protein is VP1, which forms virus-like particles that trigger the body's immune response. The virus genome is divided into early, late and non-coding control region (NCCR). Differences in the NCCR distinguish two types of JC viruses: the archetype (classical form) and the prototype (invasive form). One of the JC virus receptors is a T-cell-related glycoprotein present on the surface of most somatic cells. In addition, JC virus (JCV) is able to bind

to serotonin receptors of the SNT type, which are present on various cell types, including renal epithelium, B lymphocytes, platelets, glial cells and neurons [12]. Viral DNA is also detected in most of the aforenoted cells [11].

JC virus is widespread everywhere. Primary infection occurs in early life, most often from parent to child, and is asymptomatic. The airborne droplet and fecal-oral routes of infection are common in prolonged cohabitation through contact between people and contaminated surfaces, food and water, and the virus enters the body through the oropharynx [5]. JCV is isolated from the lymphatic tissue of the tonsils and intestines of infected individuals, which may be the sites of primary penetration, and from there the virus penetrates the epithelial cells of the kidneys, bone marrow and spleen, where it remains in a state of persistence (asymptomatic carriage). Seroconversion increases with age and reaches 60–80 % at the age of 70 years [2].

PML was a relatively unknown disease before the HIV/AIDS outbreak, when it became one of the most common opportunistic infections in this immunodeficiency syndrome. In addition, the risk of developing PML is associated with natalizumab, a monoclonal antibody used to treat relapsing-remitting multiple sclerosis. Currently, PML is an incurable disease with unfavorable outcomes, which causes difficulties in diagnosis and in the development of new immunotherapies [10]. This prompts a comprehensive study of progressive multifocal leukoencephalopathy, which will help improve diagnosis, treatment and prevention.

The purpose of the study was to conduct a clinical and morphological analysis of a fatal case of progressive multifocal leukoencephalopathy to study the etiopathogenetic features and to improve the morphological diagnosis.

Results of the study and their discussion. The 40-year-old female patient P. was under the outpatient supervision of a neurologist and a family doctor with the following diagnoses: Chronic progressive multifocal leukoencephalopathy with the development of multifocal brain damage due to pontine and extrapontine myelinolysis of the corpus callosum with the formation of gliosis zones and cystic-gliotic encephalomalacia with tetraparesis expressed in the legs and hands, sensory-motor aphasia, bulbar syndrome, severe gait disorder, neurosensory contractures in the hands, pelvic organ dysfunction (central type incontinence). He has been a group Ib disabled person since 2022.

From the medical history, it is known that the patient had been ill since 2019, when she developed spinal pain, ear swelling and a burning sensation in her head and arms up to the elbows. The patient was a smoker with a past history of genital herpes, toxoplasmosis and numerous head injuries.

The patient periodically underwent laboratory and instrumental examinations. Ig G and Ig M antibodies to toxoplasma were detected. Antibodies to HIV were not detected. CSF by PCR for HSV types I, II, VI, CMV, EMV was not detected. Other indices are within normal limits. The results of brain MRI were highlighted in the clinical diagnosis. The patient periodically underwent inpatient treatment in accordance with the diagnosis, after which the unsteadiness of her gait decreased. However, the woman's condition progressively deteriorated and the patient died shortly thereafter.

In 2013, the American Academy of Neurology proposed criteria for the diagnosis of PML [14], according to which the final diagnosis can be made on the basis of a tissue sample for histological examination or a combination of clinical and radiological data in combination with the detection of JC virus. During the patient's lifetime, no brain tissue biopsy was performed and no pathogen was detected, so the body was sent for pathological examination.

The autopsy revealed edema and hemorrhage of the dura mater. When the brain was removed, a sharply increased amount of fluid was noted. The cerebral convolutions were swollen, the border between gray and white matter was clear. The brain substance was flabby to the touch, with numerous heterogeneous foci of grayish-yellowish color in the white matter of the brain and cerebellum with a diameter of 1.2 cm or less. Changes in other organs were consistent with age.

Histological study of the brain tissue revealed perivascular, pericellular edema, perivascular infiltration with monocytes, macrophages and a small number of lymphocytes, areas of astrocytosis and enlargement of oligodendrocyte nuclei with vitreous amphiphilic inclusions (Fig.). This histological picture corresponds to changes characteristic of progressive multifocal leukoencephalopathy [1]. Therefore, the diagnosis was confirmed on the basis of clinical, radiological and pathohistological data.

Oligodendrocytes with "frosted glass" are virus-infected cells with intranuclear replication and virus accumulation. Over time, oligodendrocytes die, which is characterized by the formation of areas of demyelination. The affected areas are infiltrated by numerous macrophages that phagocytize myelin fragments [1].

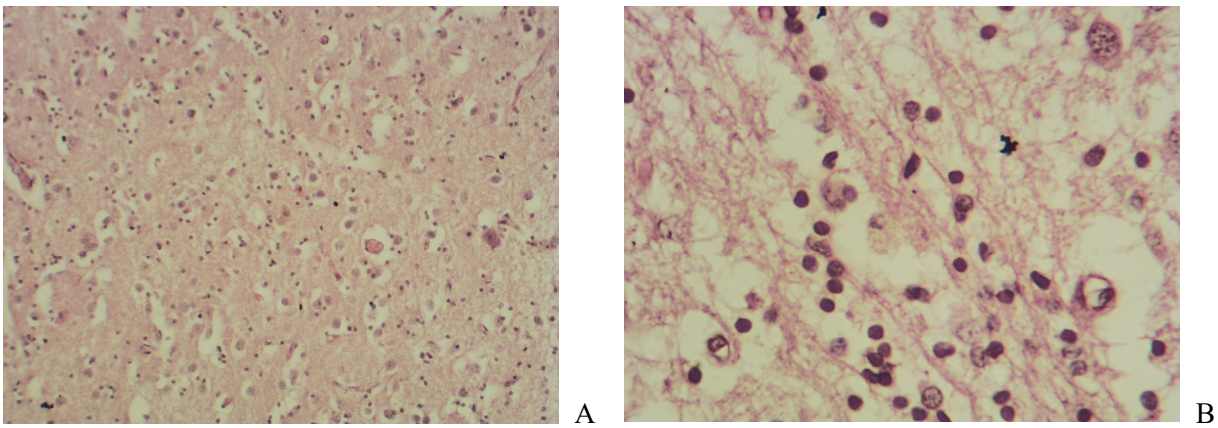

Fig. Microscopic changes in the brain of the patient with progressive multifocal leukoencephalopathy. H&E stain. a – ×100 magnification, b – ×400 magnification.

Despite the fact that the clinical diagnosis was confirmed, the question of the cause of the disease and its pathogenesis remained, since the patient did not have any classical diseases (HIV infection, multiple sclerosis) associated with the development of PML.

Publications report that reactivation of JCV with the development of PML can be observed in lymphoproliferative diseases and drug-induced immunosuppression during the use of cytostatics after organ transplantation, in the treatment of psoriasis, and Crohn's disease. Cases of PML development during treatment with glucocorticosteroids and in patients without signs of immunosuppression are also described. In addition, it was found that PML may be associated with the herpes virus HSV VI [7].

In our case, the patient had no signs of immunosuppression. Some publications indicate that PML without overt immunosuppression may account for a significant proportion of cases of this disease (11.8 %) [6, 9], and the frequency of PML without overt immunosuppression may potentially be even higher, as clinicians may not consider and verify the potential diagnosis in patients without overt immunodeficiency. It has been reported that the development of PML may be associated with comorbidities that manifest a low degree of immunosuppression, such as idiopathic CD4 lymphocytopenia, chronic renal failure, hepatitis or alcoholism [4, 8, 11]. The findings of laboratory tests revealed that the deceased did not have renal or hepatic dysfunction, lymphocytopenia and no history of alcohol consumption.

As mentioned above, there are two different types of JCV: the archetype, which is transmitted in childhood and resides in the kidneys, and the prototype (neurotropic type), which develops from the archetype and causes PML. It has been suggested that mutations that convert the archetype virus to the neurotropic form occur in the white blood cells of the bone marrow. These cells are then the source of hematogenous spread of JCV to the brain [15]. Therefore, it can be assumed that a period of dysfunction in the immune surveillance of the viral life cycle may be sufficient to allow the necessary viremia to occur in immunocompetent patients [11]. It is possible that a temporary period of immune suppression may lead to this dysfunction in immune surveillance [13].

Thus, progressive multifocal leukoencephalopathy remains an insufficiently studied disease, the study of which will be important in improving diagnosis, treatment, and thus improving prognosis.

Conclusion

Although PML is rare, clinicians should always be aware of the possibility of developing this disease with a similar clinical picture. Every patient with immunosuppression and CNS involvement should include PML in the diagnostic process. Brain MRI can be the main diagnostic clue. A biopsy should be performed to establish a definitive diagnosis. Nevertheless, much remains to be discovered and researched about PML and other polyomavirus-related diseases and their treatment. In conclusion, we would like to emphasize the importance and reliability of postmortem studies as a key element for studying and evaluating clinical quality.

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