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Case Report

Characteristic of cardiac and neurological forms of non-polio enterovirus infection

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ABSTRACT

Enterovirus infections (EVI) are ubiquitous and generally present with mild symptoms and have a favorable prognosis with full recovery. But sometimes it can be challenging to diagnose mixed forms of EVI which can result in fatal outcomes. An interesting case report on a patient admitted to the Grodno Regional infectious diseases clinical hospital. The patient was diagnosed with enteroviral infection. Histological slides of the brain, heart, lung and other systemic organs were prepared on autopsy and are presented in this scientific paper. Generalized EVI in mixed form can cause primary lesions of the brain (destructive edema), the heart (necrotizing cardiomyopathy), and sepsis while also affecting other organ systems. This can lead to unfavorable outcomes similar to that in our case report. Mixed form EVI (meningitis, myocarditis, and sepsis) can progress rapidly towards an adverse course, with the development of severe life-threatening complications. We strongly suggest that mandatory PCR screening for EVI should be carried out in young individuals with sepsis-like diseases and with a fever of unexplained origin at the time of presentation.

Keywords: Enterovirus, Viral myocarditis, Aseptic meningitis, Meningoencephalitis, Sepsis

INTRODUCTION

Enteroviruses are small, and icosahedral in shape. Enteroviruses are non-enveloped, the virions are simple, comprising a protein capsid around a single-stranded, positive-sense RNA genome. EVI is a group of acute viral diseases caused by RNA-containing pathogens of the genus *Enterovirus*. The genus *Enterovirus* belongs to the family of *Picornaviridae* and the order *Picornavirales*.[1] One of the most severe forms of EVI is generalized, which proceeds as sepsis leading to multiple organ failures and in some cases concludes with an unfavorable outcome.[2-4] Although fatal outcomes in patients with EVI are extremely rare, in the literature, cases with fatal outcomes are described, especially in children with immunodeficiency states and newborns.[3-5] The most adverse complications of EVI are encephalitis, myocarditis, and sepsis.[6-8]

The cell surfaces of the gastrointestinal tract serve as the site of the introduction of viruses into the human body, and initial replication begins in the local lymphatic tissue of the gastrointestinal tract. Then the virus enters the bloodstream, causing a short primary viremia.[1] The virus then penetrates various organs, causing the second episode of viremia within 3-7 days of illness. The infection can progress, causing severe damage to the central nervous system during the main viremic phase or at a later time. The production of antibodies by the human body in response to EVI occurs during the first 7-10 days.[2] The virus uses the proteins of the human body to synthesize viral structures by modifying the genetic factors of translation of host cells (for example, a protein that binds mRNA) and by using internal ribosome entry sites (IRES) to bypass the mechanisms of protection of host cells. Therefore, non-polio enterovirus (NPEVs) can lead to severe damage to the structure of the cell into which they are embedded.[5]

Myocarditis is a cardiac disease associated with inflammation and cell injury of the myocardium. Myocarditis in humans has been associated with several viruses. A few enteroviruses are notorious for causing cardiac injuries, for example-coxsackievirus B3 is considered a well-known causative agent. The underlying pathogenesis potentially includes the following mechanisms of injury: Excessive immune-mediated destruction of the cardiac myocytes by infiltration of immune cells targeting virus-infected cardiomyocytes or by autoimmune-mediated destruction of cardiac cells due to molecular mimicry between viral and host antigenic epitopes, or by direct virus-induced cardiomyocyte damage.[9] Outbreaks of severe forms of EVI with cardiac damage and a high frequency of deaths in maternity hospitals have been reported. Often, either the puerperal or the staff of the institutions were the source of infection. The disease can progress rapidly and has high mortality rates.[6]

Enterovirus 71 (EV-71 or EV-A71) can lead to the development of rhombencephalitis (inflammation of the brain stem, pontine tegmentum- the most common site of brainstem involvement) and the outbreak of hand, foot, and mouth disease (HFMD) as witnessed in the Eastern hemisphere (Taiwan, Japan, Malaysia, and Australia).[3,4,10] Mortality from these outbreaks had even reached 14%. At the same time, adverse prognostic symptoms were: the presence of myoclonus, lethargy, constant fever, and a maximum body temperature of more than 38,5°C.[3,4] In childhood, newborns are the most vulnerable group of patients to the development of myocarditis and encephalomyocarditis.[6,7]

Sepsis is a life-threatening multiple-organ dysfunction caused by a dysregulated host response to infection.[11] A broad range of pathogens can cause sepsis; however, bacterial infections represent the majority of cases. As high as up to 42% of sepsis presentations are culture-negative, suggesting a non-bacterial cause. Despite this, the diagnosis of viral sepsis remains significantly rare. The most common viral pathogens that can lead to sepsis are enteroviruses, Herpes simplex virus (HSV), Human parechovirus (HPeV), influenza, and dengue viruses.[8]

One such case of a severe form of EV infection was registered at the Grodno regional infectious diseases clinical hospital. The clinical and anatomical conclusion of the case: Death of child K. due to generalized EVI with a primary lesion of the brain (destructive edema), the heart (necrotizing cardiomyopathy), and sepsis.

CASE REPORT

A 2-year-old girl (Child K.) was brought to the Grodno Regional infectious diseases clinical hospital by her mother. Upon admission, she was noticed to have an increased body temperature to febrile numbers (38,5°C), the patient was lethargic, and the mother reported the patient's recent lack of appetite and periodic seizures with short-term rolling of the eyes without loss of consciousness. Child K. was immediately hospitalized. The patient had no significant social, hereditary, or surgical history.

According to the mother, the girl fell ill acutely 3 days before hospitalization in the afternoon (after coming from daycare), when the mother first noted an increase in body temperature to sub-febrile numbers (37.5°C); the child was lethargic, and there was the appearance of the small rashes under the folds of child's buttocks. The mother did not seek medical help then, and the girl did not receive treatment. 24 hours later there was an increase in temperature to febrile numbers (38.5°C), and the child had a few bouts of vomiting. She was examined by the local pediatrician and was prescribed nifuroxazide, for symptomatic relief. 24 hours after that, that is on the third day of the disease when there were no signs of improvement an ambulance was called and the emergency team administered a combination of antipyretic medications. The patient was rushed to the hospital and admitted immediately.

The 06 hours after hospitalization the general condition of the patient was severe. Body temperature was 38.3°C, and heart rate was 130/min. blood pressure was 110/60 mm Hg. Upon neurological examination, arbitrary eye movements in absence of nystagmus were noted. Periodic rolling of the eyes was pertinent and it would take 10 seconds for the fixation of the gaze. Short seizures without loss of consciousness were noted. Eye slits and pupils were equal. The face was symmetrical. Muscle tone was reduced in the upper and lower extremities. Meningeal symptoms: The stiffness of the occipital muscles was positive. A Lumbar puncture was performed demonstrating outflow of cerebrospinal fluid (CSF) under increased pressure and a CT scan was ordered which showed signs of cerebral edema, polysinusitis, and right-sided mastoiditis. Eventually, a preliminary diagnosis of meningoencephalitis of unspecified severe course with cerebral edema and convulsive syndrome was placed.

Laboratory indicators displayed initial leukocytosis, against the background of an increase in procalcitonin; hypernatremia (161 mmol / l), and azotemia (urea-14 mmol / l). Concomitant metabolic acidosis, with elevated lactate levels. The cerebrospinal fluid sample collected upon admission showed lymphocytic cytosis- 181 µl (0-5) µl; neutrophils 9; lymphocytes 91. CSF Glucose was 4.39 mmol / l (2.5-4.4) mmol / l. Minimal changes in the hemogram depicted a slight deviation toward hypo-coagulation.

The 09 hours after hospitalization the patient's condition started deteriorating rapidly, there was an increase in respiratory insufficiency, and the breathing rate was 37-42 per min. Oxygen saturation (SpO_2) dropped to 86-87%, with visible retraction of the intercostal spaces during breathing. It was decided to intubate the trachea and transfer the child to a ventilator. This was accompanied by

a sharp decline in blood pressure to 79/51 mm Hg. Infusion of norepinephrine solution was initiated at a speed of 0.23 µg/kg/min, followed by an increased dosage to 0.6 µg/kg/min. She showed no improvement leading to the addition of dopamine titration at a dose of 5 µg/kg/min, followed by increasing the dose to 10 µg/kg/min. Despite the aggressive fluid resuscitation and vasopressor therapy child, K. showed no improvement. Antimicrobial treatment for sepsis of mixed etiology was started too (Ceftriaxone 610 mg IV, constant Meropenem 480 mg by IV, Vancomycin 180 mg×4 times/day IV, Dexamethasone 2 mg×3 times/day IV, Octagam 1000 mg/kg, Acyclovir 180 mg 3 times/ day IV along with Gastroprotective therapy, cardiotonic, antipyretic, anti-edematous, sedative, anticonvulsant, infusion therapy).

The 14 hours after hospitalization the patient's condition worsened even more: a drop in heart rate to 50 per minute, a drop in pressure to 40/25 mmHg, and a drop in oxygenation SpO_2=70%, with the development of decompensated metabolic acidosis. Resuscitation measures were immediately started in full accordance with the protocol of cardiopulmonary resuscitation. Resuscitation measures lasted for 1 hour and 5 minutes and were stopped due to ineffectiveness (asystole on a cardiac monitor). Biological death was declared.

PCR results of blood and CSF samples were positive for EVI and blood sample results were also positive for EBV infection. By the time laboratory results, were processed and delivered child K. was already declared dead.

Autopsy and histopathological findings

At autopsy, on routine hematoxylin and eosin (HE) evaluation, child K. demonstrated some pertinent histopathological changes. Leptomeninges and perivascular spaces showed moderate, and brain parenchyma demonstrated severe lymphocytic infiltration (Figure 1 and 2). The myocardium showed severe lymphocytic infiltrates with hypoxic-ischemic changes (Figure 3 and 4). The remaining systemic organs showed significant HE histopathological changes as well.

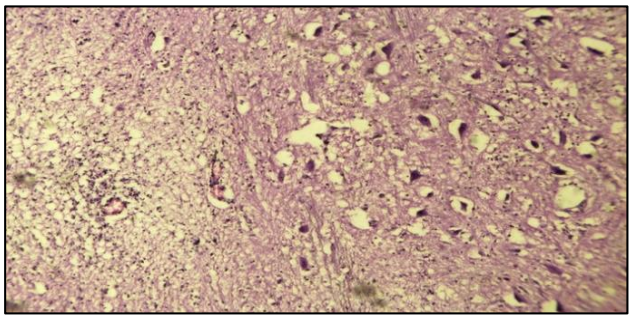

Figure 1: Histopathological analysis of autopsy of brain tissue of patient K., 2 years and 6 months. Displaying severe lymphocytic infiltration. Diagnosis: Generalized enterovirus infection. Coloring. HE of brain.

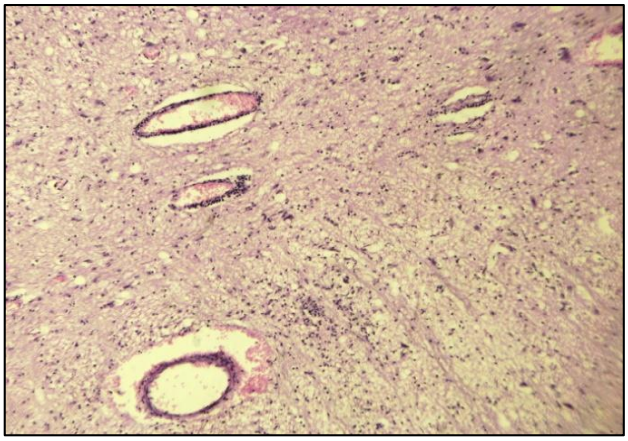

Figure 2: Histopathological analysis of autopsy of brain tissue of patient K., 2 years and 6 months. Displaying severe lymphocytic infiltration. Diagnosis: Generalized enterovirus infection. Coloring. HE of brain.

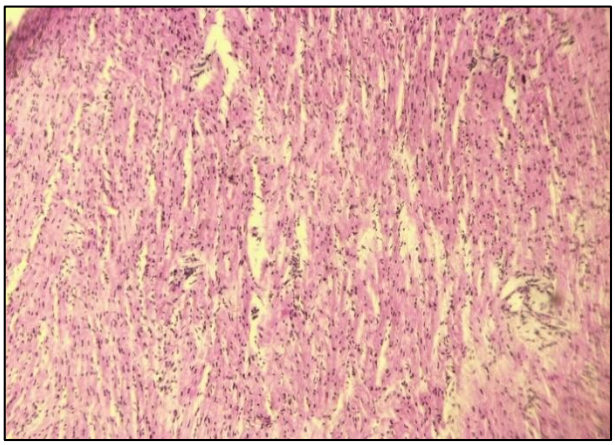

Figure 3: Histopathological analysis of autopsy of cardiac tissue of patient K., 2 years and 6 months. Displaying severe lymphocytic infiltrates with hypoxic-ischemic changes. Diagnosis: Generalized enterovirus infection. Coloring. HE of heart.

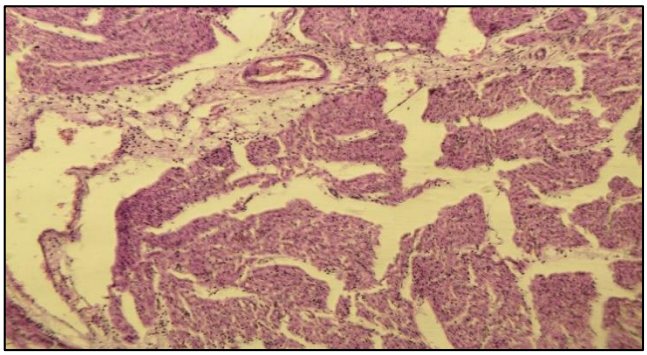

Figure 4: Histopathological analysis of autopsy of cardiac tissue of patient K., 2 years and 6 months. Displaying severe lymphocytic infiltrates with hypoxic-ischemic changes. Diagnosis: Generalized enterovirus infection. Coloring. HE of heart.

Brain changes

Figure 1 and 2 show high-resolution photographs of post-mortem preparations of the brain of child K.: Signs of encephalitis, pronounced edema, and moderate hyperemia with individual diapedetic hemorrhages. Focal areas of weak infiltration from glial, lymphoid, and macrophage elements, some regions of destructive edema without an inflammatory reaction; necrosis, and necrobiosis of nerve cells were noticed. Vascular wall necrobiosis, the presence of basophilic inclusions in the nuclei and eosinophils in the cells central nervous system (CNS); weak glial reaction, lack of perivascular couplings, and leukocytes in the foci of necrobiosis were the other pathomorphological changes.

Cardiac changes

Figure 3 and 4 show high-resolution photographs of post-mortem preparations of the heart of child K. The pathomorphological signs of acute myocarditis are shown in the figures: different thicknesses and loss of the transverse striation of the myocardial fibers are noticeable indicating hypoxic-ischemic changes. Myocardium presents with necrosis of individual fibers, and edema of interstitial tissue with the polynuclear leukocyte infiltration.

Other systemic organ changes

Extensive inflammation was observed in the histological sections of the lung. Alveolar spaces were diffusely filled with massive pink edematous fluid firmly crowded with inflammatory cells, predominantly lymphocytes, and macrophages, and diffuse thickening of alveolar walls (Figure 5 and 6). Reactive hyperplasia in mesenteric lymph nodes (Figure 7).

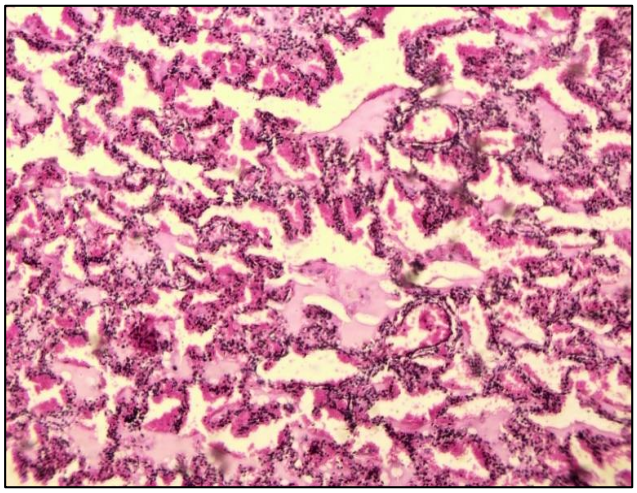

Figure 5: Histopathological analysis of autopsy tissue of patient K., 2 years and 6 months. Diagnosis: Generalized enterovirus infection. Coloring. HE of lungs. Fluid-filled alveoli engorged with inflammatory cells.

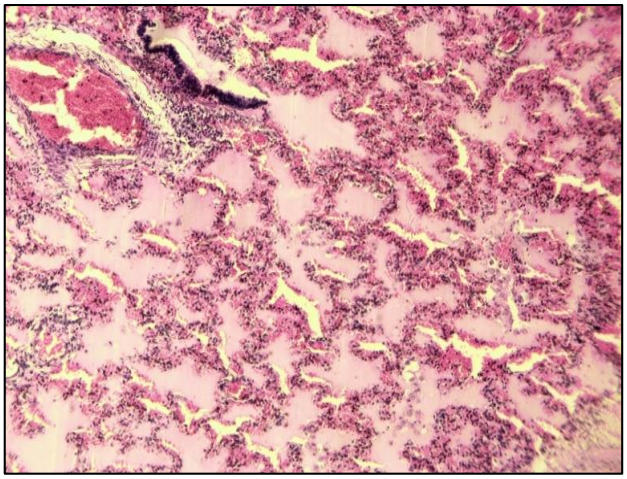

Figure 6: Histopathological analysis of autopsy tissue of patient K., 2 years and 6 months. Diagnosis: Generalized enterovirus infection. Coloring. HE of lungs alveolar spaces were diffusely filled with massive pink edematous fluid.

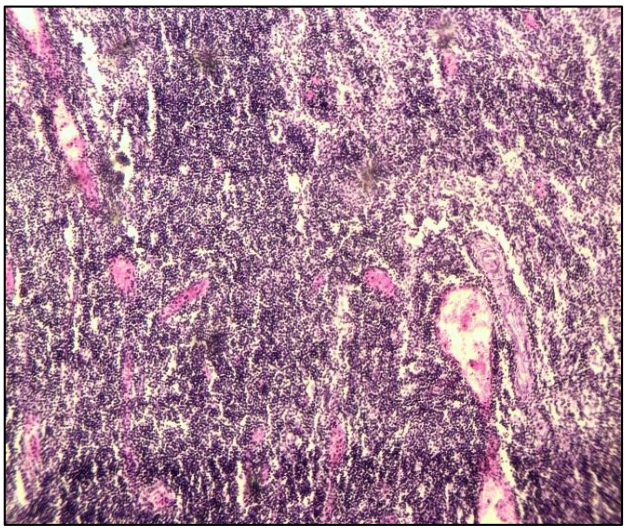

Figure 7: Histopathological analysis of autopsy tissue of patient K., 2 years and 6 months. Diagnosis: Generalized enterovirus infection. Coloring. HE of mesenteric lymph nodes showing reactive hyperplasia.

DISCUSSION

One of the most severe forms of EVI is a sepsis-like (generalized) form of EVI. This form often remains unrecognized similar to the case of child K, due to its severe course leading to multiple organ failures, it often disguises itself as "bacterial sepsis".[12] Lafolie et al in their prospective multicenter study which was conducted in numerous wards and emergency rooms in hospitals throughout France described examination of newborns (aged ≤28 days) and infants (aged >28 days to ≤2 years) with a fever of unclear origin, clinical signs of sepsis-like disease, or with signs of aseptic (serous) meningitis, as well as children (aged >2 years to ≤16 years) with

suspected meningitis. The majority of patients examined showed a positive result of PCR testing done in blood and CSF specimens. Enterovirus RNA was detected in either blood or cerebrospinal fluid in 47% of patients. Moreover, in both biological materials, the RNA of EV was determined for up to 28 days. Detection of enterovirus was more frequent in blood samples than in CSF specimens of newborn babies and infants and was less frequent in blood samples than in CSF specimens of children. Detection of enterovirus was more frequent in blood samples than in CSF specimens of infants aged 2 years or younger with fever without source or with a sepsis-like disease. Detection of enterovirus was less frequent in blood than in CSF of patients with suspected meningitis.[12]

The most susceptible populations are pregnant women, young children, older adults, and immunocompromised individuals. This heightened risk and severity are due to the relative immunosuppression present in these populations.[8] Newborns with NPEV infection are at a high risk of developing a sepsis-like condition, including meningoencephalitis, myocarditis, and hepatitis. Lethality is often high in neonates with severe EVI, especially in those complicated with myocarditis.[13] Whereas, if we talk exclusively about viral myocarditis in newborns, mortality rates can range from 30 to 83%.[14]

The main clinical symptoms of the sepsis-like form of NPEV at a given age include symptoms of malabsorption, lethargy, fever, anxiety, tissue hypoperfusion, and jaundice. The initial standard of care for all cases of sepsis, even those that are subsequently proven to be culture-negative, is the immediate use of broad-spectrum antibiotics.[8] It is almost impossible to differentiate this form of disease based on clinical signs from bacterial sepsis. One of the possible factors contributing to the severe course and unfavorable outcome of the disease in the presented case of child K. was the presence of a laboratory-verified mixed infection, DNA of the Epstein-Barr virus (EBV) was also detected in the said patient's blood. Usually, EBV infection is a typical opportunistic infection, replication of this virus indicated a state of immunodeficiency against the background of an already ongoing severe EVI infection, and, on the other hand, it also contributed to the aggravation and progression of the underlying disease. It is known that virus replication in B-lymphocytes stimulates their active proliferation and differentiation into plasmocytes. The latter secrete immunoglobulins of low specificity. At the same time, the number and activity of specific T-lymphocytes increase in the acute period of the disease. Cytotoxic T-lymphocytes inhibit the proliferation and differentiation of B-lymphocytes, destroy cells infected with the virus, and recognize virus-induced membrane antigens.[15] However, the virus remains in the body and persists in it throughout life, causing a chronic course of the disease with reactivation of the infection with a decrease in immunity.[16] It was not possible to differentiate the primary infection or activation of chronic EBV infection in this patient because of the rapid development of the clinical signs and symptoms, leading to serious complications in the body.

Nevertheless, based on the findings, disease progression, and outcome of our case, supported by histopathological findings at autopsy we propose that the presence of a mixed form of viral infection (meningitis, myocarditis, and sepsis) could contribute to a more severe course and unfavorable outcome of the disease in children. Therefore, guidelines should be formulated taking into consideration the possibilities of severe viral infections and their life-threatening complications.

CONCLUSION

EVI is a ubiquitous disease, which in most cases has a mild course. However, in certain populations that are at the highest risk (pregnant women, young children, older adults, and immunosuppressed individuals), a mixed form of EVI (meningitis, myocarditis, and sepsis) can lead to a rapid progression toward an adverse course, with the development of severe life-threatening complications. Due to the absence of definitive diagnostic criteria for viral sepsis, or protocols to at least exclude bacterial sepsis, can inevitably lead to unnecessary antimicrobial use, consequently causing antimicrobial resistance, and associated adverse effects on the host microbiome as well. We strongly suggest that mandatory PCR screening for EVI should be carried out in young individuals with sepsis-like diseases and with a fever of unexplained origin at the time of presentation.

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