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COVID-19 and EBV Co-Infection in a Child

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reported first in December 2019 in Wuhan, China. The virus soon spread all over the world and the World Health Organization (WHO) declared a global pandemic on March 11, 2020. At the beginning of the outbreak, infections were more common in adults then in children; however, in the following months, the number of pediatric infection cases increased significantly. The disease in children is less severe, but occasionally it may be complicated with Multisystem Inflammatory Syndrome. Some of the symptoms and signs may be overlapped with other infectious diseases of the childhood and confound the appropriate diagnosis. A high index of suspicion must be maintained in children while making a diagnosis. We report the case of a 5 years old presented with COVOD-19 and EBV co-infection.

Keywords

COVID-19, EBV, Pandemic, Infection, Children

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reported first in December 2019 in Wuhan, Hubei province of China. The virus soon spread through all the world and the World Health Organization (WHO) declared a global pandemic on March 11, 2020. Since then, in March 15, 2021, confirmed COVID-19 infections numbered over 119 million people worldwide and have resulted in over 2.6 million deaths. The first case of COVID-19 in children was confirmed in Shenzhen, China on January 20, 2020. At the beginning of the outbreak, COVID-19 infections were more common in adults then in children; however, in the following months, the number of pediatric infection cases increased significantly. Most cases in children are mild and treatment consists in supportive care; only a small

number need hospitalization and mortality rate is low < 0.1% of diagnosed children [1] [2] [3] [4]. As we are discovering each day more about SARS-CoV-2 infection, differences between adults and pediatric disease are probably due to changes within both immune function and the angiotensin-converting enzyme (ACE) 2 receptor, used by the virus to enter type II pneumocytes in the lung. The immune system of children is highly prepared to novel pathogens, due to high levels of innate IgM antibodies with broad reactivity, in addition to the production of the anti-inflammatory interleukin (IL)-10 by neonatal B cells [5]. Other probable explanations are alternations in T cell populations in adults due to continuous antigen stimulation and thymic involution, varied levels of ACE-2 expression in children, and the simultaneous presence of other viruses in the respiratory mucosa of children, competing with SARS-CoV-2 [6]. Besides, all this children have fewer comorbidities and a stronger pulmonary regenerative potential than adults.

2. Case Report

A 5 years old male admitted to the University Hospital Center of Tirana with a history of 2 week fever. He was treated with oral antibiotics by a local clinic for acute tonsillitis, but fever persisted and cough, diarrhea and fatigue become disturbing in the following days. No family contact with COVID-19 positive individuals was reported. On physical examination he appeared ill. The pharynx was injected with swollen tonsils without exudates. The child was tachypneic, respiratory frequency was 40 breaths/min, and oxygen saturation 94%, fine rales were found bilaterally in auscultation. Gastrointestinal manifestations consisted of abdominal pain and diarrhea. The abdomen was soft, not distended, bowel sounds were present. Nor rash on the skin, neither swollen hands or feet, were observed.

Laboratory investigations on admission revealed a blood cell count WBC 11,400 cells/mm^3 (54.7% neutrophils and 34.1% lymphocytes), RBC 4,270,000 cells/mm^3, Hemoglobin level 11.5 g/dL, Hematocrit value 33.1%, Platelet count 1,072,000 cells/mm^3, Erythrocyte sedimentation rate 28 mm/h (<15 mm/h), Aspartat aminotransferase 27 U/L (14 - 35 U/L), Alanin aminotransferase 15 U/L (9 - 24 U/L), Creatin kinase 55 U/L (30 - 200 U/L), Blood urea nitrogen 25.3 mg/dL (15 - 36 mg/dL), Creatinine 0.53 mg/dL (0.44 - 0.64 mg/dL), Serum total protein 7.9 g/dL (6 - 8 g/dL), Albumin 4.5 mg/dL (3.2 - 4.5 mg/dL), C reactive protein 1.16 mg/dL (<0.5 mg/dL), D - dimer 300 mg/dL (<198 mg/dL), Fibrinogen activity 331 mg/dL (160 - 390 mg/dL), PT quick time 106% (70% - 110%), Prothrombin time/international normalized ratio (INR) 0.96 (0.85 - 1.15), aPTT 28.7 sec (24 - 35 sec).

Abdominal ultrasonography revealed an enlarged liver 121 mm and lymphadenitis 14 × 7 mm. Chest radiography revealed bilateral peribronchial thickening and peribronchial opacities. Reverse transcriptase PCR for COVID-19 was negative, IgM antibodies for COVID-19 were positive and IgG antibodies for

COVID-19 were negative. As the child did not fulfill all the criteria to meet the diagnosis of "Multisystem Inflammatory Syndrome in Children", but the symptoms persisted and some of the inflammatory parameters were increased, there was suspected that another infectious agent could have complicated the scenery. The EBV panel result indicated acute primary infection IgM antibodies against viral capsid antigen (VCA) were positive, whereas VCA-IgG antibodies were negative.

Thrombocytosis was assumed to be of reactive origin due to excessive inflammation generated by the combination of two infectious agents COVID-19 and EBV. Once the combined diagnosis was confirmed therapeutic approach was symptomatic. Fever subsided gradually, lymphadenitis was reduced and the child appeared playful. Thrombocytosis subsided after a couple of weeks too (Table 1).

3. Discussion

As SARS-CoV-2 disease is emerging and the world is in the middle of the pandemic, it is not easy for the pediatrician, to differ between COVID-19 infection and other potential viruses of childhood. Almost all medical resources are directed towards COVID-19 infections and still it's challenging to make a diagnosis or predicts its complications in children.

It is already known that fewer cases of COVID-19 disease have been diagnosed in children than in adults. The majority of the pediatric cases have been mild, but severe illness has been reported in 2.5% of pediatric cases in China, according to the World Health Organization [7]. The most reported signs and symptoms in children are cough, pharyngeal erythema and fever. Other less common signs and symptoms include diarrhea, fatigue, rhinorrhea, vomiting and nasal congestion. A small percent presents with severe disease, dyspnea, persistent high fever, lethargy, increased levels of enzymes [4]. Since May 2020, several highly endemic countries reported a high incidence of multisystem inflammatory syndrome (MIS) in children [8] [9] [10] [11]. All include fever, elevated inflammatory markers, and organ dysfunction not attributed to another infectious cause. The median interval from COVID-19 symptom onset to MIS onset is 25 days [12]. The higher rate of positive serologic tests compared with nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR) is

Table 1. Clinical outcome of the patient.

Hositalization time	0 week	1 week	2 weeks	6 weeks
WBC	11,400 cell/mm^3	15,100 cell/mm^3	9200 cell/mm^3	8600 cell/mm^3
Lymphocytes	34.1%	51.3%	56.2%	31.4%
CRP	1.16	0.97	0.6	0.05
Thrombocytes	1,072,000 cell/mm^3	821,000 cell/mm^3	683,000 cell/mm^3	464,000 cell/mm^3
D-dimer	300 mg/dL	201 mg/dL	190 mg/dL	158 mg/dL

suggestive of a late complication of the disease [8] [12] [13] [14] [15]. Besides fever, the most common presentations of MIS are gastrointestinal (diarrhea, vomiting, abdominal pain), cardiovascular, mucocutaneous (rash, mucus membrane changes, conjunctival injection), respiratory (including sore throat), headache, and limb and periorbital edema [11] [12] [13]. Associated laboratory findings are elevated inflammation markers (neutrophilia, C-reactive protein, ferritin, erythrocyte sedimentation rate), thrombocytopenia, lymphopenia, elevated troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP), hypertriglyceridemia, and elevated D-dimer and fibrinogen (**Table 2**, **Figure 1**) [16]. Some patients meet the criteria for macrophage activation syndrome (MAS).

As the presenting child had a negative reverse transcriptase protein chain reaction (RT-PCR) for COVID-19 but a positive serology for COVID-19 (increased IgM levels, which are higher during weeks 2 - 3 of illness), prolonged fever > 10 days, cough, diarrhea, fatigue, cervical lymphadenopathy, pharyngeal erythema

Table 2. CDC case definition for multisystem inflammatory syndrome in children (MIS-C).

1) An individual aged < 21 years with
2) Clinical criteria: _ A minimum 24-h history of subjective or objective fever _ 38.0 _C AND _ Severe illness necessitating hospitalization AND _ Two or more organ systems affected (*i.e.*, cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, neurological)
3) Laboratory evidence of inflammation _ One or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils or reduced; low albumin
4) Laboratory or epidemiologic evidence of SARS-CoV-2 infection _ Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR _ COVID-19 exposure within 4 weeks prior to onset of symptoms
5) No alternative diagnosis
Abbreviations: CDC, Centers for Disease Control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

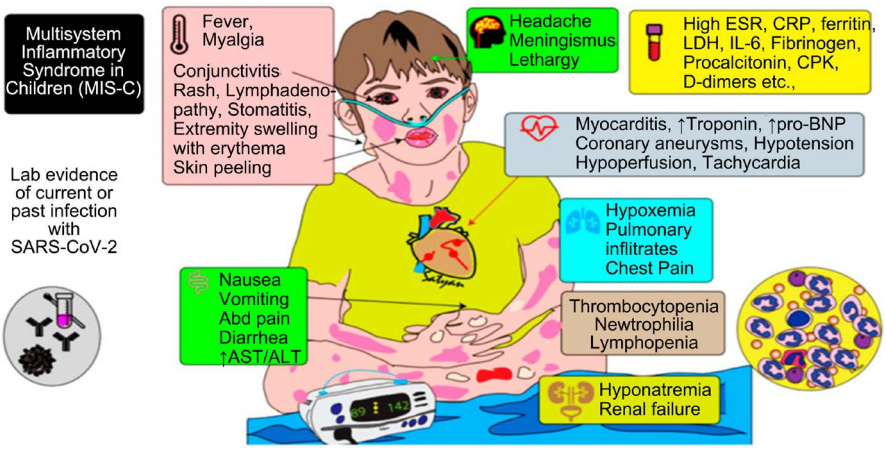

Figure 1. Infographic showing CDC criteria for the diagnosis of MIS-C.

and some of the inflammatory proteins increased such as CRP and d-Dimer, initially was presumed to be in front of a MIS-C. However there were present some confounding elements on laboratory results non consistent with MIS-C such as lymphocytosis and thrombocytosis. A consistent pattern of laboratory abnormalities has not yet been identified in children with confirmed COVID-19, however, a common laboratory abnormalities among hospitalized patients include lymphopenias (due to destruction of infected T lymphocyte cells) and thrombocytopenia in cognition with other coagulation parameters abnormalities.

On the other hand Epstein-Barr virus (EBV) which is not a rare agent causing disease in children manifests overlapping symptoms with COVID-19. EBV is ubiquitous in nature and infects a large fraction of the world population. In young children primary infection is usually asymptomatic or produces an acute illness that is often not recognized as being due to EBV or may be also presented with the full blown clinic of Infectious Mononucleosis; fever, pharyngitis, lymphadenopathy, hepato-splenomegaly and fatigue (**Figure 2**) [17]. The median duration of infectious mononucleosis is 16 days, which is much longer than the duration of most acute viral illnesses, recovery is gradual. A potent innate and adaptive immune response occurs during primary EBV infection. The innate immune system is an important first line of defense against viral infections. Many inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), IL-1β and IFN-γ are found in the sera of patients infected with EBV and COVID-19 too. IFN-γ is thought to be important for control of EBV infection [18] [19]. High levels of IFN-γ likely contribute to the symptoms experienced during infectious mononucleosis, as this cytokine is known to cause

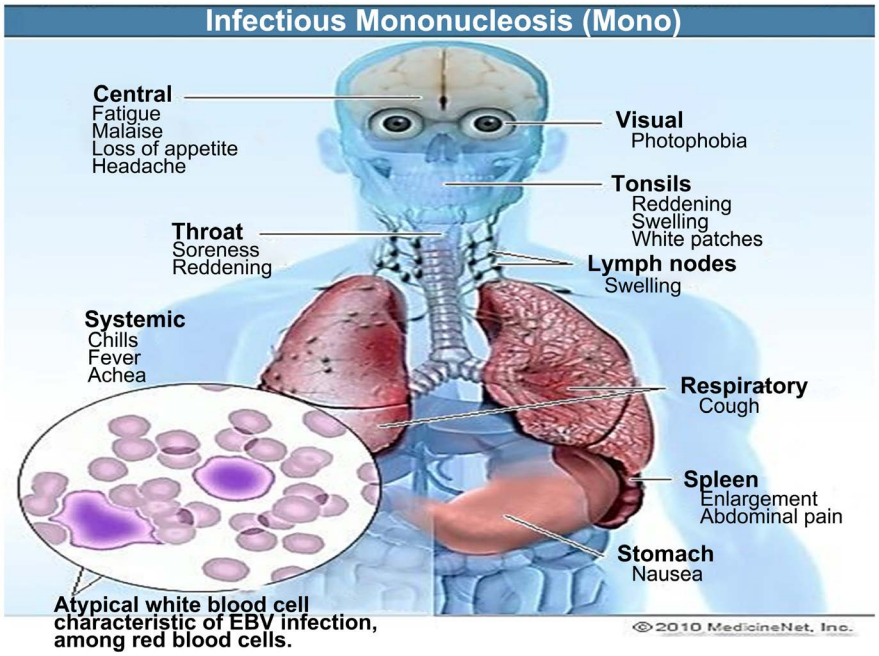

Figure 2. Infographic showing infectious mononucleosis.

headache, fatigue, and fever [20]. Both CD4 and CD8 T cells make a robust response to EBV antigens, the massive lymphocytosis in the blood that characterizes infectious mononucleosis is thought to consist largely of CD8 T cells specific for EBV lytic antigens [21]. Both agents EBV and COVID-19 modulate the immune system.

Thrombocytosis is not typical in EBV or COVID-19 infection otherwise they are companied by mild thrombocytopenia. Thrombocytosis in children are usually reactive, particularly common during recovery phase of an infection or inflammation and are usually transient and subsides when the primary stimulus ceases. Reactive thrombocytosis is usually mediated by increased release of numerous cytokines in response to infections. A wide range of cytokines may participate in the stimulation of platelet production, IL-3, IL-11, granulocyte-macrophage colony-stimulating factor, erythropoietin but the most imported role is plaid by thrombopoietin and IL-6 which are initially elevated in response to infections [22]. In this case thrombocytosis is an exaggerated physiologic response to the combined infections. Despite the strikingly high platelet count, sometimes exceeding 1,000,000 cells/mm^3, thrombotic and/or hemorrhagic complications are highly exceptional.

4. Conclusion

COVID-19 has inflicted all the world population. The number of infected children is progressively increasing. The disease in children is less severe, but sometimes it may be complicated with Multisystem Inflammatory Syndrome. Some of the symptoms and signs may be overlapped with other infectious diseases of the childhood, such as EBV and respiratory viruses, and confound the appropriate diagnosis. So a high index of suspicion must be maintained in children while making a diagnosis.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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