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Case Report

SARS-CoV-2-Induced Kawasaki-Like Multisystem Hyperinflammatory Syndrome with an atypical course in Adolescent

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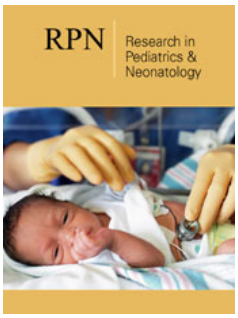

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Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, which affects both children and adults. Although most cases of COVID-19 in children have a mild course, sometimes the disease is severe. Multisystem inflammatory syndrome in children (MIS-C) is a rare complication of COVID-19, characterized by pronounced cardiovascular, gastrointestinal, and skin-mucosal signs and symptoms that, in particular, may meet the criteria for atypical or typical Kawasaki disease (KD). This article represents a clinical case of a 13-year-old boy with an atypical course of SARS-CoV-2-Induced Kawasaki-Like Multisystem Hyperinflammatory Syndrome, who was treated with intravenous immunoglobulin, corticosteroids, and aspirin. Equally, it presents a thorough description of carrying out a differential diagnosis between MIS-C and Kawasaki disease and a review of the application of drugs needed for MIS-C treatment, the main goal of which is to ensure the best protection against CA aneurysms and avoid long-term sequelae.

Keywords: Coronavirus disease (COVID-19); Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19; Kawasaki disease; Intravenous immunoglobulin (IVIG); Corticosteroids

Abbreviations: COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome; MIS-C: Multisystem Inflammatory Syndrome in Children; WHO: World Health Organization; CDC: Centers for Disease Control and Prevention; KD: Kawasaki Disease; PCR: Polymerase Chain Reaction; RNA: Ribonucleic Acid; ELISA: Enzyme-Linked Immunoassay; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CBC: Complete Blood Count; Echo-CG: Echocardiogram; TMA: Territorial Medical Association; ECG: Electrocardiogram; LV: Left Ventricle; IVIG: Intravenous Immunoglobulin; CA: Coronary Artery.

Introduction

The rapid spread of SARS-CoV-2 has led to a global pandemic among patients of all ages around the world. According to the WHO, by the end of 2022, there were 629 million cases of COVID-19 and 6.5 million deaths worldwide [1]. Global epidemiological studies of the COVID-19 pandemic indicate that the percentage of recorded cases in children is approximately 18% [2]. Although most cases of COVID-19 in children have a mild course, sometimes the disease is severe, and the clinical manifestations may differ from those in adults. Multisystem inflammatory syndrome in children (MIS-C) is a rare complication of COVID-19, characterized by pronounced cardiovascular, gastrointestinal, and skin-mucosal signs and symptoms that, in particular, may meet the criteria for atypical or typical Kawasaki disease (KD) [3-7]. Most often, this complication develops in previously healthy children aged 6 to 12 years. Early diagnosis and appropriately prescribed treatment are critical to prevent severe myocardial contractility and possible death.

Case Report

A case of an atypical course of the multisystem inflammatory syndrome (MIS-C) associated with COVID-19 in a 13-year-old boy is described below. At the end of August 2022,

the patient was hospitalized in the City Children's Clinical Hospital in the region of his residence in a severe state with complaints of abdominal pain, nausea, vomiting, sore throat, muscle pain, and significant general weakness. From the mother's words, it is known that from the first day of the disease, she noticed a high fever, and on the 7th day, a maculopapular rash appeared all over the body, including palms and soles. He was treated on an outpatient basis (amoxicillin/clavulanic acid, ibuprofen), but without significant positive effects. Physical examination upon admission: the patient is in a severe state. Temperature 39.4C, erythematous non-purulent conjunctivitis, hepatosplenomegaly, maculopapular rash, including palms and soles, "raspberry tongue", signs of cheilitis. Among laboratory tests: complete blood count on the day of admission - high level of leukocytes, lymphocytopenia, slightly increased level of platelets, high ESR; PCR (RNA of the COVID-19 virus) is negative; ELISA (IgM SARS CoV-2) - negative; ELISA (IgG SARS CoV-2) - positive; blood biochemistry tests-elevated CRP, slightly elevated levels of AST and ALT, hypoalbuminemia, elevated levels of ferritin, procalcitonin and D-dimer, troponin I - normal; coagulation tests - high level of fibrinogen, prolonged prothrombin time. Instrumental examinations: abdominal ultrasound-hepatosplenomegaly; echocardiogram-left coronary artery-3.2mm (N), right coronary artery-2.3mm (N), signs of mild mitral insufficiency, impaired contractility of the left ventricle. The patient was consulted by a cardio rheumatologist and an infectious disease specialist, after which the diagnosis was made: "Multisystem inflammatory syndrome (MIS-C) associated with COVID-19." Received treatment: Bioven 10%, amikacin, metronidazole, methylprednisolone, aspirin, Ringer's solution, physiological solution, omeprazole. During the patient's hospitalization, the complete blood count and blood biochemistry tests were performed in dynamics-the level of leukocytes remained high, and the level of platelets increased, but the levels of ESR, CRP, AST, and ALT decreased. With the improvement of the patient's condition on the 13th day of his stay in the hospital, the boy was discharged and given recommendations to continue taking methylprednisolone with a gradual dosage reduction, as well as repeat CBC, biochemistry tests (CRP) after 10 days, Echo-CG after 4 weeks.

The patient underwent further outpatient treatment for 16 days, when, after stopping taking corticosteroids, he felt a significant deterioration in his condition with the symptoms of fever, severe muscle, abdominal pain, and headaches, after which he was hospitalized the next day in the City Children's Hospital, where he was on inpatient treatment beforehand. Vital signs: temperature 38.5C, non-purulent conjunctivitis, hepatosplenomegaly. Due to the deterioration of the patient's condition, he was transferred to the "Saint Nicholas Hospital" of TMA No. 1 in Lviv on the next day (09/30) for further examination and determining the tactics of further treatment. On physical examination: the condition is severe. Hyperemia of the conjunctiva and sclera. The skin is dry, there is flaking of the skin of the fingers and toes. Heart sounds are loud and rhythmic; blood pressure=100/70mmHg. Hepatosplenomegaly. Laboratory tests: upon admission (30.09)-lymphocytopenia (12.4%, N=20-50%), mild hypochromic anemia: Hb = 10,1g/dL (N = 11-16,5g/dL), MCV=75fL (N=80-100fL), Hct=30% (N=35-50%); increased level of CRP (48mg/l), ESR (30mm/h) and fibrinogen (5.23g/l), prolonged prothrombin time (14.9sec; N=10-14sec); results of complete blood count, biochemical blood tests, coagulation tests, and urinalysis-without pathological changes. Echo-CG-the contractile function of the heart is preserved, and there is no mitral insufficiency. Abdominal ultrasound-signs of hepatomegaly. ECG-without pathological changes. Received treatment: Bioven 2g/kg once IV, methylprednisolone 1mg/kg/day, paracetamol 1g twice a day, acetylsalicylic acid 75mg once a day, Ringer's solution. Results of complete blood count after the initiation of treatment: 10/01 - lymphocytopenia (18.5%, N=20-50%), mild hypochromic anemia: erythrocytes - $3,6x10^{12}$/L (N=3,8 - 5,8 $x10^{12}$/L), Hb=9,6g/dL (N=11,0-16,5g/dL), MCV=75fL (N=80-100fL), Hct=28.7% (N=35-50%), ESR = 39mm/h; 10/02 - lymphocytopenia (16.5%, N=20-50%), mild hypochromic anemia: Hb = 10,3g/dL (N = 11,0-16,5g/dL), MCV = 75fL (N = 80-100fL), Hct = 30.7% (N = 35-50%), ESR = 50mm/h; 10/03 - lymphocytes 31.7% (N), Hb = 10,4g/dL (N = 11,0-16,5g/dL), MCV = 75.5fL (N = 80-100fL), Hct = 30.7% (N = 35-50%), ESR = 60mm/h. Blood biochemistry tests (10/03): CRP 32mg/l, other values are normal. On the 7th day of hospitalization, the patient was discharged with a significant improvement in his condition. It was recommended to continue taking aspirin at a dose of 75mg once a day for another 3 weeks and come for a follow-up examination in 2 weeks (including an echocardiogram).

Discussion

MIS-C is a disease that, due to its polymorphic clinical manifestations, creates significant difficulties in carrying out the differential diagnosis and making a final diagnosis. Therefore, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) [8,9] have defined diagnostic criteria that allow practitioners to analyze and detect this syndrome with more confidence. In the described clinical case, the diagnosis is confirmed according to most criteria: the patient is 13 years old; prolonged fever; multisystemic damage: skin-mucosal symptoms - a maculopapular rash on the whole body, including palms and soles, cheilitis, "raspberry" tongue, cardiac dysfunction-reduced LV contractility on Echo-CG, coagulopathy-increased levels of prothrombin time and D-dimer, acute gastrointestinal manifestations - abdominal pain, nausea, vomiting; signs of previously experienced COVID-19 infection. However, it must be taken into account that the absence of alternative diagnoses is necessary for the final confirmation of the diagnosis. The greatest difficulties arise when differentiating from Kawasaki disease since the clinical manifestations are very similar (the name of the multisystem inflammatory syndrome is related to this - Kawasaki-like), which can also be seen in the clinical case described by us: bilateral injection of conjunctiva; raspberry tongue; polymorphic rash on the body, as well as on the palms and soles. However, some differences need to be taken into account when establishing a diagnosis.

Therefore, the following main differences between MIS-C and KD can be distinguished: MIS-C usually affects older children and adolescents, whereas classic KD usually affects infants and young children; gastrointestinal symptoms (especially abdominal pain) are very common in MIS-C, whereas these symptoms are less pronounced in classic KD; myocardial dysfunction and shock occur more frequently in MIS-C compared to classical KD; inflammatory markers (especially CRP, ferritin, and D-dimer) tend to be more elevated in MIS-C compared to classic KD, and lymphocyte and platelet levels are generally lower in MIS-C compared to KD; CA aneurysms appear less often and regress faster in MIS-C than in KD.

One of the key points for establishing a diagnosis of MIS-C is establishing a connection with a recent SARS-CoV-2 infection. As the COVID-19 pandemic has progressed, it has become more difficult to distinguish patients with KD-like MIS-C from those with true KD as more children are exposed to SARS-CoV-2 and/or vaccinated with subsequent seroconversion. Accordingly, patient differentiation is difficult. In the case described by us, the patient has positive SARS-CoV-2 IgG, while vaccination against SARS-CoV-2 was not previously carried out. In addition, the history of the disease indicates a connection with an acute respiratory infection, the etiology of which is unknown, since the diagnosis was not carried out in time due to the patient's stay at home at the beginning of the disease, but we can assume based on positive IgG that the etiological factor is namely SARS-CoV-2. Such limitations in the early diagnosis of this viral infection create difficulties in the future for the final confirmation of the diagnosis of MIS-C. Therefore, according to the recommendations of the King's College London, the criteria for contact with COVID-19 are considered to be suspected or confirmed acute coronavirus infection 4 weeks before the development of multisystem inflammatory syndrome, probable contact with a patient with COVID-19, as well as living in areas with the unfavorable epidemic situation [10]. In addition, according to the clinical differences between MIS-C and KD, in our case, an adolescent patient with the abdominal syndrome, high levels of inflammatory markers, and lymphocytopenia can be diagnosed with "MIS-C" with greater confidence than "KD".

Importantly, any child meeting the criteria for KD (and therefore MIS-C) should be treated with intravenous immunoglobulin (IVIG) to provide the best protection against CA aneurysms. In addition, in most cases, the prescription of corticosteroids is indicated (except for the presence of contraindications or unavailability of drugs). There were four largest observational studies that differed in disease severity and inclusion criteria, treatments compared, and outcomes measured. The first three showed a greater clinical benefit with IVIG plus glucocorticoids compared with IVIG monotherapy. In our case, we used double therapy. It should be noted that in this clinical case, we can claim an atypical course of the disease: despite, at first glance, the effectiveness of the therapy during the first hospitalization, after the gradual discontinuation of glucocorticoids, the patient's condition worsened again, which required re-hospitalization and the prescription of appropriate drugs. Therefore, the duration of the disease exceeds that usually observed in MIS-C (the average duration of fever is 4 to 6 days [11]). In addition, to achieve final recovery, the introduction of IVIG in the form of two doses was required-during the first and second hospitalization, as well as the resumption of glucocorticoids after its withdrawal. The such extended treatment proved to be effective in this case, the patient was discharged in a stable condition.

In the absence of clinical improvement after dual therapy (IVIG and corticosteroids), alternative treatment options such as tumor necrosis factor inhibitors (infliximab) or interleukin-1 inhibitors (anakinra) can be considered. The use of these drugs should be carried out after consultation with pediatric rheumatologists and specialists in infectious diseases, taking into account the characteristics of each clinical case. Additional interventions depend on disease severity, clinical symptoms or physical signs, and response to initial therapy [12,13]:

A. Empiric antibiotic therapy-patients with severe multisystem involvement should generally receive immediate empiric broad-spectrum antibiotic therapy until culture results are obtained and alternative diagnoses are ruled out. In our case, the patient received amikacin during the first hospitalization until the diagnosis was clarified, after which it was discontinued.

B. Low-dose aspirin (3 to 5mg/kg per day, maximum 81 mg per day, typical treatment duration four to six weeks or until markers of inflammation [CRP, platelet count] and LV function normalize), which also was prescribed to the patient.

C. Anticoagulation therapy is prescribed for patients with severe LV dysfunction (ejection fraction <35 percent), provided the child is not at increased risk of bleeding. In less severe cases, the decision should be made individually, taking into account the clinical picture and laboratory tests and weighing the risks of thrombosis and bleeding. In our clinical case, there were no indications for the prescription of anticoagulants, so this therapy was not included.

Monitoring of cardiac function is important. The frequency of control echocardiography in dynamics depends on the clinical manifestation and cardiovascular manifestations of pathology (systolic failure, coronary artery aneurysm). In our patient with normal coronary artery function and size, a repeat echocardiogram is indicated two weeks after diagnosis to recheck CA size. Long-term follow-up data are limited, but the prognosis of MIS-C appears positive, as most children have complete clinical recovery. The overall mortality rate is approximately 1-2 percent. In most children with heart damage, the function is restored after discharge from the hospital [14]. After discharge, children with cardiac disorders must undergo follow-up cardiology monitoring.

Conclusion

Differential diagnosis of Kawasaki-like multisystem inflammatory syndrome and Kawasaki disease can be difficult,

especially in cases where there is no confirmed history of recent infection caused by SARS-CoV-2, as well as population vaccination and positive seroconversion. To establish the correct diagnosis, it is necessary to be guided by the diagnostic criteria defined by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) and take into account the main clinical differences between the diseases (age, gastrointestinal symptoms, myocardial dysfunction, inflammatory markers, and hematological indicators). The treatment of MIS-C and Kawasaki disease involves a similar pattern. Timely administration of intravenous immunoglobulin (IVIG) within 10 days of disease onset in combination with glucocorticoids and sufficient duration of treatment are key factors to ensure the best protection against CA aneurysms and avoid long-term sequelae. It is necessary to take into account the possibility of an atypical course of the disease with the occurrence of relapse and the need for re-appointment of IVIG and corticosteroids, or use of alternative therapy (infliximab, anakinra) in case of ineffectiveness of previously prescribed drugs.

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