A case of influenza A H3N2 complicated with Kawasaki disease and liver function impairment

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Case Report

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Abstract

Background: Studies have found that multiple viral infections are related to the occurrence of Kawasaki disease. It has not been reported in the world which H3N2 influenza A and Kawasaki disease occurred simultaneously. Children with influenza virus infection and symptoms associated with Kawasaki disease should be highly alert.

Case presentation: Here we present a 2-year-old Chinese girl who was treated with oseltamivir and cefoperazone sulbactam for H3N2 influenza infection and sepsis. The girl's body temperature remained high and liver enzymes increased significantly. The child was diagnosed with Kawasaki disease by a pediatric cardiologist and the patient recovered completely after being treated with gamma globulin.

Conclusion: We hope that our case report will guide clinicians to be vigilant about Kawasaki disease when high fever persists in children with H3N2 influenza.

Introduction

Influenza viruses are RNA viruses that have a strong propensity to mutate. Based on the nucleoprotein and matrix proteins, influenza viruses can be divided into four types: A, B, C, and D. Influenza A (H1N1), H3N2 (H3N2), and B (influenza B) viruses are the main viruses circulating among humans. The disease is usually self-limiting, but some patients develop severe flu due to complications such as pneumonia, which may be life-threatening. Young children under the age of 5 are at a high risk of suffering from severe influenza. Since the global pandemic of influenza A H3N2 in 1968, it is the main subtype of seasonal influenza A affecting patients globally [1].

Kawasaki disease is a systemic inflammatory disease affecting medium-sized vessel [2]. It commonly affects children below 5 years of age, including infants. The main clinical manifestations include fever, rash, conjunctival infection, mucosal congestion of the mouth and lips, cervical lymphadenopathy, edema, and desquamation of the extremities [3]. Studies have found that multiple viral infections are related to the occurrence of Kawasaki disease. In this case, influenza A H3N2 and Kawasaki disease occurred at the same time, which has not been reported in the world.

Case Presentation

A 2-year-old female was brought to our hospital on December 13, 2019, for fever of 4 days duration. Etiology was unknown. Febrile episodes occurred about 3 times a day, and the highest body temperature noted was 39.8 °C. Oral antipyretic medication was administered, which led to cessation of the febrile episodes temporarily. No accompanying symptoms were observed including cough, sputum production, or nasal congestion or colds, chills, rashes, or seizure. She was taken treatment in a hospital near the child's home where oral "children's chai gui antipyretic granules", pediatric aminophenoxanamine granules, oseltamivir phosphate granules, clarithromycin, and another unrecalled drug were administered for 1 day. She was also additionally given an infusion of ceftazidime and Chinese medicine Reduning
injection for 2 days. However, the child’s fever persisted. The patient was further observed to be weak-looking, with poor appetite and sparse stool output. Urine output remained normal. Physical examination at admission revealed a temperature of 38.4 °C, heart rate of 128 beats/min, and respiratory rate of 29 beats/min. The patient was noted to be conscious and weak-looking, with no pallor, jaundice, rashes, or petechiae. Neck examination revealed several soft, non-tender, bilateral cervical lymphadenopathies and full range of motion. Eye examination was unremarkable with no adhesions or fusion of the eyelids, or conjunctival suffusion. No pharyngeal congestion or strawberry tongue was noted. Rough breathing sounds on auscultation of both lungs, no wet rales detected. Heart sounds were strong and regular, and no murmurs were noted. The abdomen was flat and soft with no hepatosplenomegaly. Physical examination of the nervous system revealed no abnormalities. Outpatient serum examinations included a complete blood count. Leukocyte count was 13.07 \times 10^9/L (elevated), red blood cell count was 4.12 \times 10^{12}/L (average), hemoglobin concentration was 108 g/L (normal), platelet count was 422 \times 10^9/L (elevated), neutrophils accounted for 73.0% (high), and lymphocytes for 18.1% (decreased). C-reactive protein was elevated (117.40 mg/L). Serological tests for *Mycoplasma pneumoniae* were negative. Both influenza virus antigen test A and influenza virus antigen test B were negative. Chest radiography showed that both lungs were increased bronchovascular shadows. The patient was initially diagnosed with upper respiratory tract infection and sepsis. Cefoperazone and sulbactam were administered. The erythrocyte sedimentation rate was elevated (95 mm/h). B-type natriuretic peptide precursor (880.9 pg/ml), procalcitonin (1.01 ng/ml), dynamic quantitative determination of bacterial toxin (117.08 pg/ml), glutamic-oxalacetic transaminase (571.0 U/L), alanine transaminase (723.0 U/L), lactate dehydrogenase (465.0 U/L), and uroglucose (1+) were assessed. There were no abnormalities in renal function, electrolytes, creatine kinase, and creatine kinase isoenzyme. Respiratory virus nucleic acid test result was positive for influenza A H3N2. Electrocardiography showed sinus tachycardia (crying) with a T-wave notch. Abdominal ultrasonography was unremarkable. Color doppler ultrasound of the cervical lymph nodes showed bilateral cervical lymph node enlargement. The final diagnosis was influenza A and sepsis with abnormal liver function. Oseltamivir phosphate, an antiviral drug, compound glycyrrhizin intravenous drops, glualdehyde lactone, and dicyclol tablets for oral liver protection treatment were administered.

On the second hospital day, the patient developed discrete erythematous, nonpruritic, maculopapular rashes on the face, which gradually subsided. On the fourth hospital day, there was a recurrence of high-grade fever. 2D echocardiography with color doppler revealed coronary artery dilation. The child was diagnosed with Kawasaki disease by the pediatric cardiologist. The patient was treated with intravenous gamma globulin (2 g/kg), oral dipyridamole (3~5 mg/kg.d). Fever and conjunctival injection subsided the following day. Six days after admission, the child was noted to have perianal desquamation. Repeat laboratory examinations revealed the following: WBC, 9.03 \times 10^9/L; RBC, 3.81 \times 10^{12}/L; peptide, 99 g/L; platelet count, 653 \times 10^9/L; neutrophil percentage, 34.5%; and lymphocyte percentage, 48.8%. C-reactive protein level had reduced to 3.25 mg/L and erythrocyte sedimentation rate increased to 120 mm/h. The dynamic quantitative determination of bacterial toxin was 26.15 pg/mL, glutamic-oxalacetic transaminase was 30.0 U/L, glutamic-alanine transaminase was 113.0 U/L, and B-type natriuretic peptide
precursor was 1735 pg/ml. Two weeks later, the erythrocyte sedimentation rate, alanine aminotransferase and B-type natriuretic peptide precursor were normal, and four weeks later, the platelets returned to normal. By May 30, 2020, the follow-up examination of the child showed no dilation of the coronary artery, and all other examinations were normal.

**Discussion And Conclusions**

Influenza A H3N2 is diagnosed by flu-like symptoms and positive etiological test results. We herein presented a case of a child with recurrent high-grade fever and positive respiratory virus nucleic acid test for influenza A H3N2 (RNA), thereby confirming influenza A H3N2. The patient's symptoms showed no relief after oral oseltamivir and subsequently developed the following symptoms: (1) fever of more than 5 days duration with an evanescent rash; (2) hyperemia of the conjunctiva; (3) enlargement of cervical lymph nodes; (4) lip congestion, tongue papilla protrusion, or strawberry tongue; and (5) edema of the hands and feet, with the characteristic desquamation of the fingers and toes during the recovery period. Laboratory examinations revealed elevated white blood cell count (mainly neutrophils), thrombocytosis, elevated C-reactive protein level, rapid erythrocyte sedimentation rate, and high transaminase levels. Electrocardiographic abnormalities were also noted; chest plain-film radiography showed increased lung texture, and 2D echocardiogram showed a dilated coronary artery. These findings supported the diagnosis of Kawasaki disease in our case.

Kawasaki disease can cause a variety of complications. Coronary artery aneurysm is the most serious, and clinical reports of combined liver function impairment are also common. Liver function impairment is most common during the acute phase and is characterized by asymptomatic elevation of liver enzymes, cholestatic hepatitis, and gallbladder effusion [4]. The mechanism for this may be hepatic vasculitis leading to liver cell damage. Some scholars believe that it may be related to immune injury mediated by the increase in the levels of various inflammatory factors during the acute stage of the disease [5]. Both glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase were greater than 500 U/L, but with no associated clinical symptoms. Kawasaki disease with asymptomatic elevated liver enzymes was, thus, considered.

The etiology and pathogenesis of Kawasaki disease remain unclear. Some scholars believe that it is caused by the invasion of pathogenic microorganisms and an abnormal immune response in children [6]. Studies have found that multiple viral infections are related to the occurrence of Kawasaki disease [7]. Influenza-infected cells produce large amounts of proinflammatory cytokines and chemokines, such as interferon and tumor necrosis factor [8]. This massive immune response can cause a life-threatening cytokine storm. Others have suggested that tumor necrosis factor can contribute to the formation of coronary lesions and coronary aneurysm [9]. It has been described a case of KD coincident with influenza A H1N1/09 infection [10], and Jackson et al reported that Influenza B virus was associated with KD [11].

This case occurred during the influenza pandemic season. It is unclear whether the abnormal immune response induced by the H3N2 influenza A virus resulted in the occurrence of Kawasaki disease or
whether this was a case of co-infection of H3N2 influenza A and Kawasaki disease. There are no reports regarding this phenomena locally or internationally; thus, it warrants further studies.

Our case highlights the importance of immediate and prompt identification of Kawasaki disease in children presenting with unremitting fever. Children diagnosed with influenza virus infection should be evaluated for accompanying symptoms related to Kawasaki disease; laboratory examinations should be conducted to identify the elevated white blood cell count and C-reactive protein, progressive elevation of platelet counts, and poor response to antibiotic treatment. Especially for patients with significantly increased liver enzymes, attention should be paid to distinguish whether the children have symptoms of liver function injury, and alert to asymptomatic elevated liver enzymes. It is necessary to be vigilant in assessing a patient for the complications of Kawasaki disease to ensure prompt diagnosis and treatment, as lack of prompt management may lead to severe adverse consequences.

Influenza A H3N2 combined with Kawasaki disease is very rare in clinical work, especially in patients with asymptomatic increased liver enzymes. If a patient develops similar symptoms, the pediatrician should be on high alert to prevent serious consequences.

Declarations

Ethics approval and consent to participate

The requirement of ethical approval and consent for this case report were waived due to the retrospective nature of the study by the ethics committee of Children's Hospital Affiliated to Zhengzhou University.

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Availability of data and materials

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Author contributions

CLG provided the case. CLG and YYW wrote initial drafts of the manuscript. CLS and YBC reviewed and edited subsequent drafts of manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not Applicable.

Consent for publication

Written informed consent was obtained from the child's guardian for this case report. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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