Case Report

Febrile cholestasis with mucocutaneous signs in a 13-year old during COVID-19 pandemic: a forgotten intravenous immune globulin response.

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Abstract

Intravenous immune globulins (IVIG) are increasingly used in Kawasaki-like cases possibly related to coronavirus disease 2019 (COVID-19), generally with striking clinical response. We describe a teenager presenting febrile cholestasis, along with coronary aneurysm and other criteria fulfilling incomplete Kawasaki disease. The girl was treated with high dose acetylsalicylic acid and IVIG transfusion. Laboratory work-up revealed hepatitis antibodies. However, this result was obtained after IVIG and is considered as passively transferred IgG's from blood donors. Especially during COVID-19 pandemic, clinicians should be familiar with unusual Kawasaki presentations as febrile cholestasis, as well as inconclusive serology after the desired IVIG therapy.

Introduction

Kawasaki disease (KD) is the most common pediatric systemic vasculitis, mostly affecting children under five years (1). KD typically presents as a self-limited condition, with fever and other acute inflammatory manifestations. Coronary arteritis leading to coronary artery aneurysm is the most important complication. The frequency of aneurysm development and mortality of KD has dramatically decreased with intravenous immune globulin (IVIG) therapy. Etiology of KD remains unknown, although some infectious agents are considered as triggers in genetically predisposed individuals (1). During the COVID-19 pandemic, in April 2020, clinicians in the United Kingdom noted an increasing number of previously healthy children presenting with a severe inflammatory syndrome with Kawasaki features (2). All 8 reported cases tested positive for SARS-Cov-2 antibodies. On May 14th, the Centers for Disease Control and Prevention (CDC) issued a public health advisory and case definition, terming it Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 (3). Other authors refer to the entity as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (3).

Case report

On May 16th, a 13-year-old girl was admitted to our pediatric department with protracted fever for five days. She complained of swollen fingers and generalized pruritus. In the past week, she experienced two episodes of presyncope when standing up. Her medical history included prematurity, short bowel resection secondary to fulminant necrotizing enterocolitis and yearly iron infusion for iron deficiency anemia. She took weekly vitamin D supplementation as only medication. She was in general good health and had no known contacts with SARS-Cov-2 virus. Clinical examination revealed a moderately sick teenager with diffuse polymorphous exanthema, icteric sclerae, strawberry tongue and crackled lips. Extremities showed mild edema, but no desquamation. Neither lymphadenopathies nor enlarged liver were palpated. Upon presentation, she was hemodynamically stable with a blood pressure of 100/56 mmHg, body temperature 38.0°C. Laboratory examination showed elevated inflammatory parameters: erythrocyte sedimentation rate 54 mm/h (ref. range < 20 mm/h) , C-reactive protein 23.2 mg/L (ref.range <5 mg/L), leucocyte count 11.4 x10E9/L (ref. range 4.3-11.0 x 10E9/L), with decreased lymphocyte count 0.4 x10E9/L (ref. range 0.97-3.96 x 10E9L). Thrombocyte count was normal, ferritin levels were at 110 µg/L (ref. range 13-78 µg/L). We noted discrete hypo-albuminemia 34 g/L (ref. range 35-55 g/L). Prothrombin time was prolonged (INR 1.2) with elevated fibrinogen and D-dimers. Liver enzymes aspartate aminotransferase and alanine aminotransferase were only mildly elevated, contrasting with marked elevation of total bilirubin up to 87.2 umol/L (ref. range <17.1 umol/L) and gamma-glutamyl transferase 227 U/L (ref. range <21 U/L). Alkaline phosphatase remained within the reference range.

Throat swab was negative for streptococcal infection. Urine sample showed a moderate sterile pyuria. Abdominal ultrasound revealed no hepatic or biliary abnormalities. Echocardiography showed inflammation of the left coronary artery with proximal fusiform aneurysm. (Fig1). We considered this case as strongly suspicious for MIS-C, although CDC definition was not fulfilled because of negative SARS-Cov-2 polymerase chain reaction (PCR) on nasopharyngeal swab. The patient was hospitalized and intravenous immunoglobulins (IVIG, Nanogam®) were administered at dose regimen 2g/kg. Respecting coronary aneurysm, acetylsalicylic acid was started at anti-inflammatory dose (50 mg/kg daily). After initiation of IVIG, rapid clinical improvement was seen with gradual normalization of all clinical as well as biochemical anomalies. Vital signs remained stable during hospitalization. Considering differential diagnosis for jaundice, viral hepatitis serology was investigated on a second blood sample. It revealed hepatitis B surface antibodies along with hepatitis B core antibodies and positive hepatitis E IgG antibodies. All hepatitis IgM antibodies were negative. Given that she was vaccinated following the Belgian scheme and had no history of hepatitis infection, this was a particular result. Retrospective analysis of the blood sample prior to IVIG administration, however, showed absence of any hepatitis antibodies. SARS-Cov-2 antibodies turned out to be negative as well.

Repeated echocardiography showed slightly decreased coronary abnormalities. The patient was discharged after five days with continuation of acetylsalicylic acid at antithrombotic dose (2 mg/kg daily). Ambulatory follow up, including pediatric cardiology and hepatology, was provided.

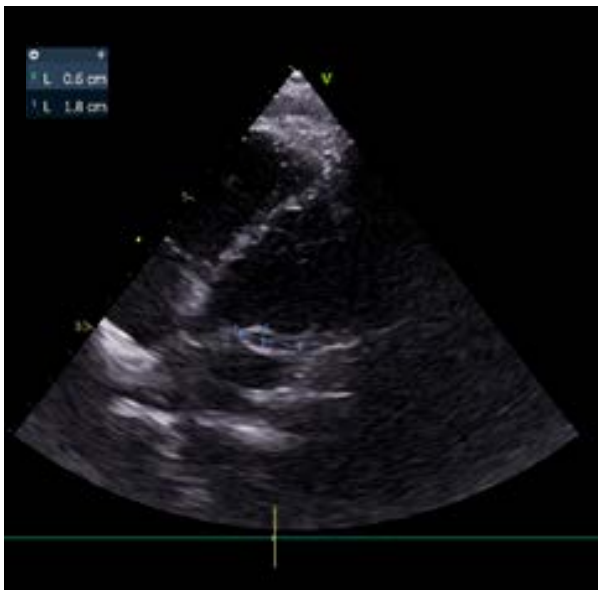
Discussion

This case broaches two important observations. Firstly, we describe a Belgian teenager presenting with Kawasaki-like disease during COVID-19 pandemic. Presenting with fever lasting for five days and presence of 3/5 major clinical signs of KD, diagnosis of incomplete Kawasaki disease can be established (1). Laboratory parameters (hypo-albuminemia, coagulopathy, pyuria) as well as echocardiographic abnormalities support this diagnosis. On the other hand, clinical as well as biological course is largely parallel to other reported cases of multisystem inflammatory syndrome associated with COVID-19 (2,3). Contrasting with many others, our patient did not need intensive care. We believe prompt recognition and initiation of IVIG treatment might be a partial explanation, but also MIS-C likely representing a spectrum of disease (3). Our case meets most criteria for MIS-C following CDC definition: individual aged <21 years presenting with fever, laboratory evidence of inflammation, clinical severe illness requiring hospitalization, multisystem organ involvement (cardiac, hematological, dermatological and hepatic) and no other plausible diagnosis. There was no evidence for current or recent SARS-Cov-2 infection by PCR nor serology. Nonetheless, we believe our case to be related to COVID-19 considering Belgian epidemiological situation at time of diagnosis, characteristic lymphocytopenia and the -otherwise rarely- KD in a teenager (1,4). Negative serology is noted in some other suspected reports as well (3). As expected in MIS-C, the girl responded stunningly to IVIG therapy.

Secondly, our patient presented cholestasis with conjugated hyperbilirubinemia up to 87 umol/L at time of diagnosis. Although not widely recognized among clinicians, acute febrile cholestasis is associated with Kawasaki disease in up to 20% of the cases (5). To exclude viral origin, we performed hepatitis serology which showed hepatitis B and E IgG-antibodies. We note that this result was obtained after initiation of IVIG therapy. Initial blood sample being negative for all hepatitis antibodies, cholestasis in our patient is presumably related to KD. This hypothesis was reinforced by gradually declining cholestatic parameters during hospital stay.

Human immune globulins are antibody-containing products purified from large pools of human plasma (6). The WHO has published minimum standards for manufacturing IVIG preparations. Preparation should contain highly purified polyvalent IgG from at least 1000 individual donors, undergoing viral inactivation processes among many others. Following European guidelines, Belgian blood services use triplet HIV/HBV/ HCV nucleic acid testing in blood product donors (7). Consequently, subjects with prior hepatitis B infection (negative hepatitis B surface antigen, no HBV DNA but anti-hepatitis B surface and anti-hepatitis B core IgG) are eligible donors.

Figure 1 : *Left coronary artery inflammation with proximal fusiform aneurysm at diagnosis in our patient. Measurements: 1.8 x0.6 cm (May 16th, 2020)*



Hepatitis E (HEV) on the other hand is a fecal- orally transmitted RNA-virus. Seroprevalence in blood donors in European countries varies from 2 to 49% and is rising during the past 10 years (8,9). After acute infection, hepatitis E IgG's are probably lifelong detectable but do not protect against re-infection. HEV transmission with blood transfusion is described, but not with IVIG. HEV RNA is currently not tested in blood donors in Belgium, although recent data support this practice (9). In conclusion, hepatitis epidemiology and blood donor screening strategy in Belgium, can explain the presence of hepatitis B as well as hepatitis E IgG's in IVIG preparations.

As illustrated, IgG serologic studies can become falsely positive after IVIG therapy due to passively transferred antibodies (6). Considering IgG's half-life of 21 to 28 days, these antibodies should not persist beyond 60 days. Indeed, in our case, there was absence of hepatitis B core and hepatitis E IgG on laboratory testing a few months later. Quantification of hepatitis B surfaces antibodies was at 5 IU/L (ref. range after vaccination >10 IU/L). We conclude that our patient is a non-responder to routine vaccination, therefore we planned a hepatitis B booster vaccination.

Conclusion

During the first months of COVID-19 pandemic pediatricians worldwide noticed a rising number of Kawasaki-like cases, some exhibiting severe multisystem inflammation requiring intensive care. We faced the case of a teenager also suffering from acute cholestasis and coronary aneurysm. All clinical criteria as defined by the CDC for Multisystem Inflammatory Syndrome in Children (MIS-C) were met. Following timely recognition and initiation of IVIG therapy, the girl demonstrated a rapid and complete recovery. Through diagnostic work-up, we encountered positive hepatitis B and E antibodies that were passively transferred by IVIG and had no clinical impact.

This case thus highlights two important learning points:

- Febrile cholestasis as a presentation of Kawasaki disease in up to 20% of cases.
- The importance of diagnostic antibody testing prior to IVIG administration. We warn clinicians for drawing incorrect serologic conclusions thereafter due to passive transfer of IgG's.

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