Atypical Hemolytic Uremic Syndrome in a Post-COVID-19 Child: Its Differential Diagnosis with COVID-19, Multisystemic Inflammatory Syndrome and Outcome

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Abstract

Pediatric Multisystemic Inflammatory Syndrome (MIS-C) is one of the most severe manifestations of SARS-CoV-2 in pediatrics [1]. This is a report of MIS-C with clinical presentation in infants with atypical Hemolytic Uremic Syndrome (aHUS).

Keywords

MISC, COVID-19, aHUS, Children, Critical Care

1. Introduction

COVID-19, a disease caused by a new coronavirus called SARS-CoV-2, was initially related to involvement only of the respiratory tract, affecting mainly adults. Subsequently, as the pandemic progressed, clinical manifestations were observed in children, predominantly mildly. In April 2020, the Royal College of Paediatrics and Child Health in the United Kingdom issued an alert reporting a new clinical presentation in children and adolescents associated with COVID-19 [1]. After the alert, several other countries began to report similar clinical manifesta-
tions, which was later named as Multisystemic Inflammatory Syndrome associated with COVID-19 (MIS-C) [2] [3]. Since then, several other serious and potentially fatal manifestations of COVID-19 in pediatrics have been observed, in addition to Acute Respiratory Syndrome (ARS) and MIS-C [4] [5] [6]. As an example, the temporal relationship of atypical Hemolytic Uremic Syndrome (aHUS) with COVID-19 [4] has been described, speculating whether SARS-CoV-2 may be the infectious trigger for the manifestation of the syndrome. In this clinical case, the authors describe aHUS related to COVID-19 with a clinical presentation similar to MIS-C, discussing the difficulties in interpreting the relationships of these nosological entities.

2. Case Report

We report a case of a 2-year-old female infant with a severe and atypical clinical evolution of SARS-CoV-2. The patient had presented abdominal pain and fever. Two days later, she developed diarrhea, prostration, drowsiness, dyspnea, and oliguria. On presentation she was pale, hypotensive, appearing with dyspnea, anasarca, hepatosplenomegaly, stomatitis with bleeding lesions, seizures, and coma (Glasgow Scale 6). Orotracheal intubation was performed, continuous adrenaline infusion was titrated, and ceftriaxone was administered. The child has a previous diagnosis of COVID-19, confirmed by real-time polymerase chain reaction (RT-PCR), ten days before starting the first symptoms. The admission and evaluation laboratory tests are shown in Table 1. The exams were visualized: normal echocardiogram computed tomography of the chest with consolidative opacities with air bronchograms, and predominantly peripheral "frosted glass" opacities. Initial differential diagnoses included (MIS-C), atypical Hemolytic Uremic Syndrome (aHUS), COVID-19 complicated with sepsis, septic shock, and Disseminated Intravascular Coagulation (DIC). In the initial evolution, the patient presented renal failure and arterial hypertension and, later, evolved with hypotension and anuria, when the association of dobutamine with norepinephrine was installed and hemodialysis was initiated. The main diagnostic hypothesis was raised as aHUS, however, the differential diagnosis with MIS-C was proposed, even though the time interval between the current disease and the diagnosis of COVID-19 was only 10 days. In addition, the presence of schistocytes in peripheral blood was visualized (Figure 1 & Figure 2), in addition to haptoglobin < 6 mg/dl and normal C3 and C4 complement. Due to the absence of clinical response to the aHUS and previous exposure to SARS-CoV-2, the diagnosis of MIS-C was reconsidered, and immunoglobulin (IVIG) 2g/kg associated with methylprednisolone (30 mg/kg) was performed on the 5th day of hospitalization. Eculizumab was not initiated due to the unavailability of the medication in Brazil. The child evolved with refractory septic shock, disseminated intravascular coagulation and multiple organ dysfunction, evolving with death on the fifteenth day of hospitalization.
Table 1. Evolution of laboratory tests.

| Tests                | D1<sup>§</sup> | D3<sup>§</sup> | D5<sup>§</sup> | D10 | D15  |
|----------------------|----------------|---------------|---------------|-----|------|
| Hb (g/dL)            | 7.6            | 14.5          | 8.3           | 6.8 | 10.3 |
| HT (%)               | 21.5           | 40.2          | 23.5          | 20.4| 30.2 |
| Leukocytes (µ/L)     | 26.400         | 33.900        | 33.600        | 16.700| 3.360|
| Thrombocytes (µ/L)   | 51.000         | 31.000        | 26.000        | 76.000| 114.000|
| Reticulocytes (%)    | 0.6            | 2.5           | 3.6           | 2.0 | 3.6  |
| PT (%)               | 17.8           | 49.4          | 64.0          | 71.3| 71.0 |
| PTT (sec)            | 30.0           | 21.0          | 34.0          | 20.9| 28.3 |
| Fibrinogen (mg/dL)   | 233            | 175           | 140           | 205 | 210  |
| pH                   | 7.28           | 7.10          | 7.26          | 7.16| 7.19 |
| Bicarbonate (mEq/L)  | 14.2           | 10.3          | 11.4          | 18.7| 13.8 |
| BE                   | -11.0          | -18.4         | -13.7         | -10.3| -13.5|
| Lactate (mmol/L)     | 6.7            | 16.2          | 17.0          | 5.0 | 17.0 |
| D-dimero (ng/mL)     | >10            | 6.69          | 2.28          | 0.94| 1.09 |
| LDH (UI/L)           | 999            | 990           | 798           | 1278| 999  |
| CPK (U/L)            | 141            | 44            | 23            | 38  | 26   |
| CKMB (U/L)           | 30             | 27            | 42            | 27  | 62   |
| Urea (mg/dL)         | 261            | 278           | 228           | 121 | 64   |
| Creatinin (mg/dL)    | 4.7            | 4.6           | 3.18          | 2.04| 1.65 |
| Sodium (mEq/L)       | 141            | 137           | 133           | 136 | 131  |
| Potassium (mEq/L)    | 5.6            | 5.6           | 3.5           | 3.8 | 2.6  |
| Albumin (g/dL)       | 2.0            | 2.2           | 2.5           | 2.1 | 1.9  |
| CRP (mg/dL)          | 102.0          | 63.8          | 23.8          | 71.0| 166.6|
| ESR (mm/h)           | 50             | 68            | 30            | 24  | 110  |
| Triglycerides (mg/dL)| 288            | 97            | 103           | 182 | --   |
| Uric acid (mg/dL)    | 14.3           | 10.5          | -             | -   | --   |
| Troponin (ng/mL)     | <0.1           | <0.1          | <0.1          | <0.1| <0.1 |
| Coombs test          | +++            | +             | ++            | +   | ++   |
| Ferritin (µ/L)       | 677.1          | -             | -             | -   | -    |
| AST (U/L)            | 62             | 27            | 31            | 36  | 2    |
| ALT (U/L)            | 77             | 35            | 13            | 40  | 30   |
| GGT (U/L)            | 14             | 12            | 15            | 29  | 20   |
| BT (mg/dL)           | 0.44           | 0.27          | 2.55          | 4.22| 5.92 |
| BD (mg/dL)           | 0.12           | 0.07          | 1.81          | 2.93| 3.96 |
| BI (mg/dL)           | 0.32           | 0.2           | 0.74          | 1.29| 1.96 |

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| Test                | Value       |
|---------------------|-------------|
| C4 (mg/dL)          | 14          |
| C3 (mg/dL)          | 103         |
| Haptoglobin (mg/dL) | <6.0        |

Hb: hemoglobin; Ht: hematocrit; PT: prothrombin time activity; PTT: partial thromboplastin time; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CKMB: creatine kinase-myocardium dimers of type B; C-RPC: reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; BT: total bilirubin; BD: bilirubin direct bilirubin; BI: indirect bilirubin.

Figure 1. Schistocytes in peripheral blood (H & E - 40×).

(a)
Figure 2. Chest CT scan images: (a) Bilateral ground glass opacities and consolidations—axial plane; (b) Bilateral ground glass opacities and consolidations—sagittal plane; (c) Bilateral ground glass opacities and consolidations—coronal plane.

3. Discussion

The authors describe this case in order to expand the speculations of SARS-CoV-2 as the infectious trigger, as well as other viruses, in the triggering of inflammatory syndromes, emphasizing the effects of the cytokine cascade. Based on the data presented above, it can be observed that there was systemic thrombotic microangiopathy, which may occur by activating the alternative complement pathway, both in the aHUS and in the MIS-C. On the other hand, aHUS may be triggered by viral diseases, including respiratory viruses, such as influenza, as described in the literature [5]. Some authors suggest adding COVID-19 as a trigger factor for triggering or recurrent of aHUS [6] [7].

At the same time, some similarities between aHUS and MIS-C raised the possibility of the patient presenting MIS-C, according to the following criteria: ga-
intestinal tract involvement (vomiting and diarrhea), hematological (anemia, leukocytes, thrombocytopenia, mild changes in prothrombin time), changes in oral mucosa (stomatitis), renal failure, hypotension, but without myocardial dysfunction. The tests also demonstrated the similarity between conditions such as leukocytes with neutrophilia, anemia and thrombocytopenia, an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, D-dimer, ferritin, lactic acid dehydrogenase (LDH), creatine kinase (CK) but without significant changes in cardiac enzyme like or creatine kinase-myocardium dimers type B (BNP).

Due to the previous SARS-CoV-2 infection, clinical symptoms led to need to differentiate aHUS with COVID-19. However, children with COVID-19, usually, do not evolve with inflammatory syndromes, except when had been complicated with bacterial infection, sepsis and septic shock or MIS-C.

In the pathophysiology of aHUS and COVID-19, it is known that both conditions activate the ACE-2 and Gb3 membrane receptor to trigger the chain of reactions responsible for the manifestations of both diseases, despite the greater tropism by the kidney in aHUS and respiratory system in COVID-19. The final pathway of both is the cytokine cascade that leads to inflammation and thrombotic events, which even occurs in MIS-C. In this context, it is possible to speculate that although they are nosologically different entities, it is possible that SARS-CoV-2 may have a triggering role of aHUS, as well as in MIS-C [8].

Acute respiratory failure and systemic coagulopathy may occur in COVID-19, due to microvascular injury mediated by the complement route, although this is not the most common evolution of SARS-CoV-2 infection in children, and MIS-C is more compatible with symptoms of microvascular alterations, leading to inflammation and subsequent multiple organ dysfunction [9].

Nevertheless, aHUS may be associated with complications in organs other than the kidneys, such as lungs, colitis and paralytic ileus, pancreatitis, changes in the central nervous system and multiple organ dysfunctions, complications observed in the case reported. According to the literature, such complications may be better evidenced after 14 days of evolution, as observed in the reported patient, who presented more serious complications in the second week of evolution [5].

In this case, the infection occurred one month before hospitalization, when the child presented mild respiratory symptoms, coinciding with ten days of evolution when the symptoms of aHUS began, which would still be an early evolution of MIS-C. The clinical similarity of the two syndromes may have in common, in addition to the clinical presentation and similar pathogenic mechanisms, the triggering by a previous infection by SARS-CoV-2.

Initially, the authors found the relationship of aHUS triggered by COVID-19 in two descriptions, one in a 32-year-old adult female with a prior history of recurrent atypical aHUS and the other in a 16-month-old child recently reported as the first pediatric case [10] [11]. Subsequently, new cases have been described,
increasingly emphasizing the relationship between SARS-CoV-2 and aHUS [7] [12].

Other conditions, usually triggered by viruses, such as diabetes, have already been described as related to SARS-CoV-2 and, possibly, other conditions may be related, requiring greater attention from pediatricians in the face of these conditions usually related to the virus as a trigger, as already described for H1N1 influenza [13].

The diagnostic hypothesis of MIS-C was also less robust, because it is a condition that compromises fewer infants, being more commonly diagnosed in older age groups, especially schoolchildren and adolescents. The hypothesis of aHUS was the most evidence, being, at the first moment, related to the infection predicted by SARS-CoV-2. Unfortunately, due to the severity of the child’s evolution, it was not possible to perform the pulmonary biopsy, and the postmortem examination was not authorized by the family.

4. Conclusions

This report demonstrates the importance of the differential diagnosis of systemic inflammatory conditions caused by SARS-CoV-2, as well as their severity, which leads to the need for ICU admission and early intervention due to the chances of death.

With the report of the current case, the authors emphasize that patients with COVID-19 are at potential risk of developing virus-induced diseases, especially those with uncontrolled complement activation, such as MIS-C and aHUS. Early diagnosis and treatment can reduce morbidity and mortality.

Conflicts of Interest

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

References

[1] Multisystemic Inflammatory Syndrome in Children and Adolescents Likely Associated with COVID-19: An Acute, Severe and Potentially Fatal Presentation. https://www.sbp.com.br/fileadmin/user_upload/22532d-NA_Sindr_Inflamat_Multsisistemica_associada_COVID19.pdf
[2] Panupattanapong, S. and Brooks, E.B. (2020) New Spectrum of COVID-19 Manifestations in Children: Kawasaki-Like Syndrome and Hyperinflammatory Response. Cleveland Clinic Journal of Medicine, 1-7. https://doi.org/10.3949/ccjm.87a.ccc039
[3] Capone, C.A., Subramony, A., Sweberg, T., Schneider, J., Shah, S., Rubin, L., et al. (2020) Characteristics, Cardiac Involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection. The Journal of Pediatrics, 224, 141-145. https://doi.org/10.1016/j.jpeds.2020.06.044
[4] Hansen, M., Van Quekelberghe, C., Kunzmann, S., Visciani, G. and Latta, K. (2021) COVID-19 and Atypical Hemolytic Uremic Syndrome in Infants. Nieren- und Hochdruckkrankheiten, 50, 385.
[5] Wu, Q., Xing, Y., Shi, L., Li, W., Gao, Y., Pan, S., Wang, Y., Wang, W. and Xing, Q.
(2020) Coinfection and Other Clinical Characteristics of COVID-19 in Children. Pediatrics, 146, e20200961. https://doi.org/10.1542/peds.2020-0961

[6] Ville, S., Le Bot, S., Chapelet-Debout, A., et al. (2021) Atypical HUS Relapse Triggered by COVID-19. Kidney International, 99, 267-268. https://doi.org/10.1016/j.kint.2020.10.030

[7] Dalkıran, T., Kandur, Y., Kara, E.M., et al. (2021) Thrombotic Microangiopathy in a Severe Pediatric Case of COVID-19. https://doi.org/10.1016/j.kint.2020.10.030

[8] Salbuski, A., Nehus, E.J., Jodele, S. and Ricci, K. (2022) Diagnostic Considerations in H1N1 Influenza-Induced Thrombotic Microangiopathy. Journal of Pediatric Hematology/Oncology, 44, e237-e240. https://doi.org/10.1097/MPH.0000000000002036

[9] Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp

[10] Li, J., Wang, X., Chen, J., Zuo, X., Zhang, H. and Deng, A. (2020) COVID-19 Infection May Cause Ketosis and a Ketoacidosis. Diabetes, Obesity and Metabolism, 22, 1935-1941. https://doi.org/10.1111/dom.14057

[11] Kim, N.Y., Há, E., Moon, J.S., Lee, T.H.H. and Choi, E.Y. (2020) Acute Hyperglycemic Crises with Coronavirus Disease-19: Case Reports. Diabetes & Metabolism Journal, 44, 349-353. https://doi.org/10.4093/dmj.2020.0091

[12] Khandelwal, P., Krishnasamy, S., Govindarajan, S., et al. (2022) Anti-Factor H Antibody Associated Hemolytic Uremic Syndrome Following SARS-CoV-2 Infection. Pediatric Nephrology, 37, 2151-2156.

[13] Gill, J., Hebert, C.A. and Colber, G.B. (2022) COVID-19-Associated Atypical Hemolytic Uremic Syndrome and Use of Eculizumab Therapy. Journal of Nephrology, 35, 317-321. https://doi.org/10.1007/s40620-021-01125-8