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Case Presentation

COVID-19 Associated Multisystem Inflammatory Syndrome with Skin Lesions after Induction in Acute Myeloid Leukemia in a Pediatric Patient

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ABSTRACT

Severe SARS-CoV-2 infections in pediatrics are rare and usually presented as Multisystem Inflammatory Syndrome in Children (MIS-C). There are few descriptions about pediatric oncology patients. We describe a case of 5-year-old male with Acute Myeloid Leukemia (AML).

He presented febrile neutropenia with skin lesions and progressive clinical worsening. He had positive RT-PCR test for SARS-CoV-2 and criteria for MIS-C. He received methylprednisolone, immunoglobulin and granulocyte colony stimulating factor. Anti-interleukin 6 was administrated due to severe lung disease and refractory to treatment, presenting response and slow clinical recovery. Chemotherapy was restarted, he didn't present relapse during treatment and has no sequelae of COVID-19. Severe SARS-CoV-2 infections in pediatrics are rare and presented as Multisystem Inflammatory Syndrome in Children (MIS-C). There are few descriptions about pediatric oncology patients. We describe an Acute Myeloid Leukemia (AML) patient who presented COVID-19 complicated by MIS-C. He had slow clinical recovery and was able to resume AML treatment.

Keywords: SARS-CoV-2; Multi-system inflammatory syndrome; Pediatric leukemia; Tocilizumab

INTRODUCTION

Clinical presentation of COVID-19 is described as a spectrum, from asymptomatic patients to severe forms [1-3]. The correlation of severity with host immune response had been extensively discussed, from innate to adaptive immunity, highlighting inflammatory cytokines in severe forms [4]. Severe pediatric infections are less expressive [5,6]. However, a severe of inflammatory disorder related to COVID-19 in children was nominated Multisystem Inflammatory Syndrome (MIS-C) [7]. Among adult population, cancer is risk factor and hematologic malignancies have higher mortality while pediatric cancer is rare and this population has its own specific characteristics [8-12].

We describe a case of a child previously diagnosed with Acute Myeloid Leukemia (AML), evolving with fever associated to skin lesions during neutropenia period. He was diagnosed with SARS-CoV-2 infection and MIS-C [13-18].

CASE PRESENTATION

Retrospective case report data was collected from medical record from a Brazilian reference pediatric cancer institution. It was approved by the ethical committee of the Federal university. The patient's family gave written informed consent for publication.

A 5-year-old male was admitted to hospital after presenting petechiae for 3 months, for further investigation and treatment. Bone marrow analysis showed AML M2 subtype (FAB), without recurrent cytogenetic abnormalities. He had absence of infiltration of central nervous system. He started induction therapy, according to AML BFM 2004 protocol, standard risk, receiving high dose chemotherapy (cytarabine, idarrubicin and etoposide). After 4 days he presented febrile neutropenia, without complications. Despite high spectrum antibiotic therapy, he maintained fever for 4 days and developed cutaneous rash. Blood and urine cultures were performed and were negative. Biomarkers (serum galactomamnan) for fungal infection were also negative. After 4 days of antibiotics, he became afebrile for 6 days, and then presented again high

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temperature (38.5°C). It was associated with progressively worsening of cutaneous lesions which were biopsied. Its analysis resulted in perivascular lymphocytic infiltration and lymphocytic vasculitis, negative for bacterial, fungal and viral search. Additionally, he had cough and diarrhea. Inflammatory markers raised (C reactive protein-CRP: 124 mg/L (Reference Range (RR)<1); Fibrinogen: 446 mg/dL (RR 200-400); D-dimer: 1500 ng/mL (RR<500); Interleukin-6 101 pg mL (RR 1,5-7,0)) and RT-PCR (Real Time Polymerase Chain Reaction) for SARS-CoV-2 was positive, leading to criteria for MIS-C. He received methylprednisolone (2 mg/kg), standard Intravenous Immunoglobulin (IVIG) (2 g/kg), while being transferred to Intensive Care Unit (ICU). He developed acute respiratory distress, which needed intubation with protective ventilation; renal failure with continuous hemodialysis and myocardial dysfunction, receiving hemodynamic medications, including levosimendan. On the 4th day after worsening, a single dose of tocilizumab (8 mg/kg) was administrated, presenting rapid laboratorial response with drop of CRP inflammatory levels, from 303 on day of application to 124 two days after. D-dimer and interleukin-6 started reducing on the third day after medication. He had no adverse effects from the drug. The patient also received Granulocyte Colony Stimulating Factor (GCSF) (5 mcg/kg/day) because of its severe neutropenic condition. Platelet transfusion was necessary almost daily for 15 days; no adverse effect was identified associated with transfusion. Enoxaparin was only used indicated when platelets level were higher than 50,000. Red blood transfusion was also necessary. The clinical recovery was slower than laboratory response. He had gradual respiratory and hemodynamic improvement and extubation was performed after 27 days on ventilation. He needed recovery from withdrawal syndrome and was able to be discharged from hospital 57 days after admission. A bone marrow aspirate showed complete morphologic remission, 40 days after chemotherapy cycle. He was evaluated on follow up consultations, with good performance. The first RT-PCR negative for SARS-CoV-2 was on day 49 after de 1st positive test. It was considered safe to resume AML treatment after the second negative test and he completed chemotherapy cycles. Periodic follow ups show no evidence of sequelae of COVID-19. Despite the pause on treatment, he did not present relapse of leukemia (Figure 1).

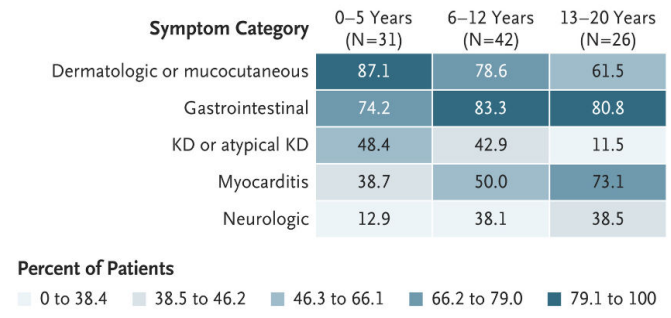

Figure 1: Syndrome clusters according to age group among patients with Multisystem Inflammatory Syndrome in Children (MIS-C).

RESULTS AND DISCUSSION

Severe presentations of SARS-CoV-2 infection have heterogeneity among different populations. MIS-C is a severe form of infection in children and adolescents, characterized as fever longer than 3 days, documented SARS-CoV-2 infection and involvement of at least two systems: Skin, gastrointestinal, respiratory, cardiovascular, hematologic, neurologic and renal.

MIS-C management involves immune modulation, which indicates the use of glucocorticoids and IVIG. Tocilizumab is a monoclonal antibody anti-IL6, which bounds its receptor and blocks inflammatory mediation. This medication was already used in rheumatologic disorders and appeared to show success also on MIS-C treatment. There is no contraindication for leukemia patients. Retrospective studies have suggested that tocilizumab may be associated with lower risk of death or intubation in patients with severe COVID-19 pneumonia [19,20]. In this case, it was considered that tocilizumab contributed for inflammation reduction. As he had severe neutropenia secondary to high dose chemotherapy, due to the severity of infection, GCSF was used to accelerate white blood cells increase, leading to a contribute to immune regulation. The patient had slow clinical recovery due to all damage that cytokine release had done.

A study enrolling 1,116 patients younger than 21 years with MIS-C or severe COVID-19 had no case of oncology patient described. Regarding pediatric leukemia patients with SARS CoV-2 infections, there are a great proportion of mild infections reported, when compared to adults, even with febrile neutropenia. Systematic review reinforced the presumption of good outcome, presenting 15 deaths in 226 patients [21]. However, complications are more frequent than in the general pediatric population. A multicenter Brazilian study found higher mortality in children treating cancer (12.3%) than in the general pediatric population (1%) [22]. Patients with AML are assumed to have higher risk of COVID-19 complications, as they have a myelosuppressed status and myeloid dysfunction, but it is not fully seen among pediatric population. A UK's Coronavirus Monitoring project did not find a worse outcome in children with hematological malignancies and COVID-19, when compared to solid tumors [23,24]. Severe COVID-19 onsets in children undergoing leukemia treatment have been described, and they had successful recovery when treated for MIS-C [25-27].

CONCLUSION

In this case, there has been a struggle to achieve COVID-19 diagnosis, as he was hospitalized for a while, been accompanied by his mother the whole period. The infection source was not elucidated. Moreover, several diagnoses were considered. These children are under chemotherapy and their severely compromised immune status can lead to innumerous complications, which can have clinical presentations that mimic MIS-C. Infectious complications are highly discussed in cancer. Especially among AML patients, there is concern about several bacterial, viral and fungal infections. Also, there are chemotherapy related complications, like cytarabine induced cutaneous eruptions, from acral erythema to vacuities like

presentation. Negative serology can be a confusion factor in these patients, when having deeply compromised immune status, and is not a good diagnostic tool. With the overlap of symptoms, the clinical suspicion is the most important.

Even with the advent of vaccines and improvement of the pandemic, it is unlikely that SARS-CoV-2 will vanish. Therefore, we will still have to deal with severe cases in future, and a child with weakened immune status could be a target for this infection for a long time. It must be considered in neutropenic complications, especially when involving multiple systems.

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