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MULTISYSTEM INFLAMMATORY SYNDROME IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Paediatrics

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ABSTRACT

Leukemia is the commonest malignancies encountered in the paediatric population, out of which Acute Lymphoblastic Leukemia (ALL) is the commonest type. It is one of the curable malignancies if picked up early and treated promptly. If left untreated, it causes bone marrow failure leading to immunosuppression, further leading to higher risk of infections and further complications. The Coronavirus disease-19 (COVID-19) pandemic has been a catastrophe affecting all age groups worldwide. The paediatric population has been relatively spared from the active COVID-19 infection, although multisystem inflammatory syndrome occurring after SARS-CoV-2 infection is seen in children. The illness presenting as fever with rash with multiorgan involvement may have a much worse course and prognosis in immunosuppressed children.

We report a 12 year old male child who presented with fever, rash, cardiogenic shock and multiorgan failure which was diagnosed as acute lymphoblastic leukemia complicated with multisystem inflammatory syndrome after SARS-CoV-2 infection. He had severe anaemia and thrombocytopenia along with multiorgan involvement involving the cardiovascular, neurological, gastrointestinal, mucocutaneous and renal systems. He was treated with glucocorticoids but failed to respond to treatment and had rapid deterioration and eventually succumbed to his illness.

KEYWORDS

Multisystem inflammatory syndrome in children (MIS-C), Paediatric inflammatory multisystem syndrome (PIMS), post-COVID complications, Leukemia

INTRODUCTION

Acute lymphoblastic leukemia accounts for nearly 60% cancers found in children and adolescents. ALL has a peak incidence at 2-5 years of age and has a male predominance [1]. It is classified into two types phenotypically, 85% cases are B-lymphoblastic leukemia, 15% are T-lymphoblastic leukemia and approximately 1% are derived from mature B cells. B-ALL carries better prognosis. [2,3] Survival rates of children with ALL have improved over the past few years, especially in the developed countries owing to early diagnosis and chemotherapy. If left untreated, it leads to bone marrow failure and further complications which can be fatal. Patients with leukemia are at higher risk of infection due to bone marrow failure as well as while receiving treatment with chemotherapy or corticosteroids which are used during induction remission. Multisystem inflammatory syndrome in children is an immune mediated complication triggered by the SARS-CoV-2 infection occurring 2-6 weeks after the active infection. When compared with otherwise healthy children, it may have a more fulminant course, like any other infection, in a child with leukemia.

CASE REPORT

A 12 year old male child, born of non consanguineous marriage presented with swelling of bilateral lower limbs which had gradually increased over a period of one month, high grade fever since five days and difficulty in breathing since two days. On examination, he had tachycardia (Heart rate of 144 beats/minute) and respiratory distress (Respiratory rate of 60 breaths/min) with severe subcostal and intercostal retractions, oxygen saturation of 85% on room air, blood pressure of 90/56mm of Hg (below 50th percentile for age). He also had severe pallor, icterus, bilateral pitting pedal oedema and generalized lymphadenopathy along with petechiae all over the body. [Figure 1 & 2] On per abdomen examination, child had hepatosplenomegaly, liver 5cm palpable below right costal margin, firm with smooth surface and rounded edges with a span of 10cms and spleen 3cm palpable below left costal margin. He was drowsy with Glasgow coma scale of 14/15. Oxygen therapy was started and child was admitted to intensive care unit. Initial resuscitative measures were carried and a blood workup including arterial blood gas analysis were sent. Blood gas analysis was suggestive of uncompensated metabolic acidosis. Complete blood count revealed severe anaemia with haemoglobin of 2.5gm%, leukocytosis with total counts of 46,100/cubic mm with differentials of N=4%, L=87%, E=1%, M=2% and severe thrombocytopenia with platelet count of 13,000/ml. Hyponatremia was present (126mEq/litre). Liver function test done, were within normal limits. Renal function test was suggestive of hyperuricemia (8.2mg/dL). Prothrombin time and activated partial thromboplastin time were within normal limits. Peripheral blood smear revealed more than 5% blast cells. Hence, samples sent for flow cytometry keeping leukemia as the first differential diagnosis. Fever work up sent which was not suggestive of any fever focus. Given the current scenario, COVID-19 infection was also ruled out.

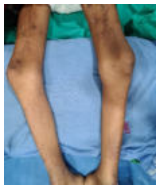

Figure 1: Petechiae on bilateral lower limbs

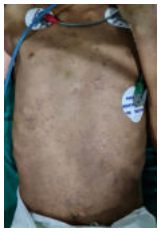

Figure 2: Petechiae over chest and abdomen

Injectable ceftriaxone and other symptomatic treatment started. Allopurinol @12mg/kg/day was started in view of hyperuricemia. Shock was refractory and did not respond to isotonic saline boluses, hence, dopamine infusion was started @10micrograms/kg/minute. Two dimensional echocardiogram was done which suggested poor left ventricular function with left ventricular ejection fraction (LVEF)=40%. Child received multiple transfusions of packed cells and platelet concentrate. Despite this, respiratory distress worsened and repeat blood gas analysis showed worsening of metabolic acidosis. Adrenaline infusion was started @0.3mcg/kg/min. Child was electively intubated and put on ventilatory support. Sodium

bicarbonate correction was given as per calculated base deficit. He had one episode of generalized tonic clonic seizure within 24 hours of admission for which he was loaded on fosphenytoin @30mg/kg followed by maintenance @7.5mg/kg/day. He continued to have continuous high grade fever spikes. Antibiotics were stepped up to a combination of piperacillin-tazobactum and amikacin. Blood cultures did not grow any pathogenic organism. SARS CoV-2 antibodies were sent after ruling out other causes of fever which were positive with titres >10. Serum ferritin and D-dimer were sent which was grossly elevated.

Flow cytometry revealed B-cell acute lymphoblastic leukemia. CSF analysis was done which revealed no blast cells in CSF to rule out nervous system metastasis. Injection dexamethasone @5mg/square meter was started for remission induction as well as for treatment of MIS-C. Prophylactic anti-viral and anti-fungal drugs were added.

In the due course, child had multiple convulsions and was loaded on levetiracetam @20mg/kg.

Further, the child went on to develop pulmonary and gastrointestinal bleeding. He was repeatedly transfused with packed cells and platelet concentrate. Injection vitamin K was given for 3 days. After some improvement in clinical status, inotropes were gradually tapered. Serial CBCs showed some improvement in haemoglobin and platelet count with normalization of total counts. Chemotherapeutic agents vincristine (@1.4mg/sq meter once a week), daunorubicin (@60mg/sq meter once a week) and L-Asparginase (10,000 units/sq meter twice a week) started for remission induction under monitoring. After the first cycle, he did not show any clinical improvement. The pulmonary and gastrointestinal bleeding restarted and urine output reduced to below 1ml/kg/hour suggesting multi organ failure. He continued to have convulsions. A CT brain was done which suggested intra cranial bleed involving the cerebellum, brainstem and thalamii. Child did not respond to treatment. He had a sudden cardiac arrest, cardiopulmonary resuscitation was attempted but the child could not be revived.

DISCUSSION

Leukemia is the commonest malignancy encountered in the paediatric population out of which acute lymphoblastic leukemia (ALL) is the commonest type. Early recognition and treatment of ALL carries better prognosis. [2,3] If left untreated, bone marrow failure occurs, which leads to immunosuppression which increases susceptibility to infections. Infections which may have a mild course in otherwise healthy children, may have an unpredictable and fulminant course in such children. Also, glucocorticoids and chemotherapeutic agents used for treatment further contribute to the immunosuppression. [4,5]
The Coronavirus disease-2019 pandemic has been catastrophic worldwide although the paediatric population has been relatively spared. Some of these children present with Paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 infection (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C). In April 2020, 8 cases of multi system inflammatory syndrome were reported for the first time in the United Kingdom who presented with fever, shock and elevated inflammatory markers with no significant past history or co-morbidities. [6] In May 2020, Centre for disease control (CDC) issued a national health advisory regarding guidelines for diagnosis of MIS-C. [7]

The exact pathophysiology and data regarding why MIS-C occurs only in some children after the SARS-CoV-2 infection is still not completely understood.

A study was carried out in United States from March to May 2020 where 186 children under the age of 21 years who were previously healthy, with no underlying co-morbidities were diagnosed as MIS-C. Most patients (71%) had involvement of 4 organ systems; most common being gastro-intestinal (92%), cardiovascular (80%), haematological (76%), mucocutaneous (74%) and respiratory (70%). About 80% of these patients required intensive care unit out of which 20% even required invasive mechanical ventilation. The mortality was approximately 2%. [8]

In our case, the child had fever which lasted for more than 3 days along with 3 criteria (rash, shock and coagulopathy) along with elevated inflammatory markers, after ruling out bacterial sepsis and other causes of fever with positive antibody titres fulfilling the criteria for MIS-C given by the World Health Organisation. Although some of these features overlap with his underlying condition i.e. acute lymphoblastic leukemia such as cutaneous lesions and shock making the diagnosis tricky.

Only one case of MIS-C in a newly diagnosed case of acute lymphoblastic leukemia, which is similar to our case, has been reported so far. The child had a similar presentation but milder symptoms and had presented to the hospital at an early phase and was treated with glucocorticoids. [9]

The treatment of ALL consists of 4 phases: remission induction, consolidation, intensification and continuation. Glucocorticoids are capable of inducing apoptosis in the malignant cells thus making them a central component in the treatment of ALL in the remission induction phase. On the other hand glucocorticoids or intravenous immunoglobulin are the treatment options in cases of MIS-C.

Studies have been carried out regarding the treatment options for MIS-C and the efficacy of various options. One major study which was carried out in 614 children from 32 different countries suffering from MIS-C which concluded that there is no significant difference in outcomes with either glucocorticoids or with intravenous immunoglobulins. [10]

Our patient presented to the hospital at a very late stage when bone marrow failure with congestive cardiac failure and severe bleeding manifestations had set in. The deterioration was more rapid due to associated complication with post-SARS-CoV-2 multisystem inflammatory syndrome.

CONCLUSION

Owing to the ongoing COVID-19 pandemic, MIS-C should be kept as a differential diagnosis for fever with rash with multiorgan involvement especially in a rapidly deteriorating child with an underlying immunosuppressive condition such as leukemia.

Infections in such immunocompromised patients require aggressive management as they can have rapid deterioration and may still carry poor prognosis.

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