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A case of Acute myeloid leukemia complicated by post COVID-19 multi-system inflammatory syndrome—children

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A B S T R A C T

Corona Virus disease 2019 (COVID-19) pandemic has presented a huge challenge to the health care system in terms of magnitude of cases and to pediatric oncology units with varied clinical presentations. Acute myeloid leukemia (AML) is a rare heterogenous cancer of childhood with an induction mortality around 15% in our country due to neutropenic sepsis. Multisystem inflammatory syndrome in children (MIS-C) is an hyperinflammatory syndrome seen 4–6 weeks after COVID-19 infection. COVID infection in some of these children would have gone unnoticed. Here we report a two year eight months old boy diagnosed with AML on induction chemotherapy developed post COVID MIS-C. Here we discuss a child with AML on induction chemotherapy who developed very high-grade fever spikes which later was diagnosed as post COVID MIS-C.

2. Case report

A 2-year 8-month-old boy presented to us with ten days history of intermittent fever, swelling of feet. On examination he was febrile, pale, conscious and alert. He had hepatomegaly, no palpable lymphnodes, or splenomegaly. Other systemic examinations were unremarkable. The patient’s blood investigations revealed a hemoglobin of 7.2g/dl, total leukocyte count (TLC) of 54,000 cells/mm³, platelets of 17,000 cells/mm³, peripheral smear examination showed 50% blasts. Bone marrow aspiration showed suppressed hematopoiesis with >60% blasts. Flow cytometry revealed blasts with CD34+ve, CD 123+ve, CD 38+ve, CD7(subset), CD117+ve, CD33+ve, CD13+ve, HLADR, CD65(dim)+ve, cytoplasmic MPO +ve. The cytogenetics revealed inversion of chromosome number 16 (inv16). His cerebrospinal fluid(CSF) examination was positive for malignant cells. He was diagnosed as a case of Acute Myeloid leukemia with inv(16)(p13.1q22) (AML with recurrent genetic abnormalities as per WHO classification) with CNS positive status [7]. FLT 3 mutation was negative. He was initiated on chemotherapy as per AML-15 protocol - induction therapy with no etoposide (DA 3 + 10-daunorubicin and cytosine arabinoside). He received twice a week triple intrathecal therapy (methotrexate, hydrocortisone and...
cytocrine arabinoside) until two consecutive CSF samples were negative for malignancy.

The child developed fever and loose stools on day 8 of induction chemotherapy. His complete blood picture (CBC) showed hemoglobin of 7.1 g/dL, TLC of 100 cells/mm³. Neutrophils-0 cells, platelets of 11,000 cells/mm³. He was given packed red cells and single donor platelet transfusions and was initiated on intravenous (IV) cefaperazone-sulbactum and amikacin. He continued to have fever despite IV antibiotics. On day 3 of febrile neutropenia, as he had high spikes of fever with worsening of general condition, IV meropenem was substituted instead of cefaperazone-sulbactum and last dose of injection cytocrine arabinoside on day 10 was omitted. He was on itraconazole fungal prophylaxis due to underlying leukemia and intense chemotherapy would have itraconazole fungal prophylaxis since the beginning of chemotherapy. His two blood cultures were negative at this stage.

The patient continued to have high grade fever spikes of 103-104 °F on day 13 of induction and body temperature didn’t touch the baseline for 30 h (Fig. 1). At this stage the child was miserable but hemodynamically stable. TLC remained at 100 cells/mm³ with 0 neutrophils, platelets were 18,000 cells/mm³, serum lactate was normal. The chest radiograph was normal, and ultrasonogram of abdomen did not reveal any source of infection.

Non-infectious causes of fever were suspected at this stage, especially post-COVID MIS-C. There was no history of exposure or infection with COVID-19 before. He was given intravenous immunoglobulin (IV Ig) 2 g/kg as he continued to have fever. His COVID IgG titers, serum ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), interleukin-6 (IL-6) were sent for testing. However, as he continued to have high fever spikes, 12 h after IV Ig, the child was started on high dose dexamethasone 10mg/m²/day in two divided doses. The reports showed ferritin of 2600 ng/ml (7-140 ng/ml), IL 216 (0-7 pg/ml), CRP – 52 mg/L(<5 mg/L), LDH 320 U/L, albumin 2.5 g/dl, COVID IgG antibody titre 17 (<1 is non-reactive). The child became apyrexial within 6 h of starting steroids and it was continued for 2 more days (Fig. 1). The child developed erythematous maculopapular rash all over his body further. Two-dimensional echocardiogram didn’t reveal any coronary artery dilatation but showed mild serous effusion. His CSF flow-cytometry was negative for malignancy. He successfully completed his 2 courses of induction and has just completed the two courses of high dose cytarabine consolidation.

3. Discussion

Febrile neutropenia is an oncological emergency, more so during induction phase of AML chemotherapy. Prompt initiation of antibiotic therapy after sending appropriate cultures is of paramount importance in its management [8]. MIS-C is a novel clinical entity with a clinical overlap with Kawasaki disease, Toxic shock syndrome. WHO diagnostic criteria incorporate a wide range of symptoms from cardiac abnormalities to gastrointestinal symptoms. It is associated with elevated inflammatory parameters like ferritin, lactate dehydrogenase, interleukin-6, C-reactive protein [Table 1] [6].

Our patient presented with febrile neutropenia on day 8 of induction and he was started on appropriate antibiotic therapy. It is very common to have gram negative sepsis or fungal blood stream infection leading to persistent fever spikes during induction. Starting high dose dexamethasone during severe neutropenia is a difficult decision, but in our patient due to non-subscidence of fever an inflammatory etiology was suspected with post COVID MIS-C being our first differential owing to the epidemiological and temporal association with the SARS-CoV2 pandemic. The biochemical parameters were also supportive of our diagnosis of MIS-C. Though there was no history of COVID in this child or his family 4 weeks ago, he did have fever and myalgia which the family and we thought were part of his AML symptoms. During this current pandemic any unusual presentation or unexplained fever one needs to be highly suspicious of MIS-C [9]. Even though there is no confirmatory test for MIS-C, the clinical picture, biochemical parameters, and response to steroids make post-COVID MIS-C a likely diagnosis.

Hiwarkar et al. reported a case of refractory Acute myelomonocytic leukemia M5 referred for transplant who presented with fever, gastrointestinal symptoms and cardiac manifestations. Their patient responded to high dose steroids [10]. Immune disequilibrium due to underlying leukemia and intense chemotherapy would...
be responsible for manifestations of such hyperinflammatory syndrome. High index of suspicion is needed in such cases as immunosuppressive therapy can be lifesaving.

**Conflict of interest**

The authors have no conflict of interest to declare.

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**Patient’s Consent**

Consent was obtained from the parents for publishing the case.

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