CASE REPORT

# Unique Challenges Faced by a Child with Standard Risk Leukemia in Post-COVID Era: A Case Report

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## Abstract

Children with malignancies are facing new challenges in post-COVID-19 era. We report an interesting case of a child on treatment for acute lymphoblastic leukemia having a very protracted course of illness with complications not often seen with standard therapy. It intends to make pediatric oncologists and intensive care specialists wary of potential newer complications.

**Keywords:** Coronavirus disease-2019, Leukemia, Multisystem inflammatory syndrome in children, Tuberculosis.

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## Introduction

The coronavirus disease-2019 (COVID-19) infection is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Children are affected by sequelae in the form of multisystem inflammatory syndrome in children (MIS-C) which is a hyperimmune state resembling illnesses as Kawasaki disease, toxic shock syndrome, or macrophage activation syndrome. Diagnosing MIS-C in children with cancer receiving immunosuppressive therapy or having febrile neutropenia is quite challenging. There is dearth of data on complications and course of MIS-C in pediatric oncology patients.

We report an interesting case of 3-year-old child on treatment for precursor B acute lymphoblastic leukemia (pre-B ALL) with MIS-C, pulmonary tuberculosis (TB), and posterior reversible encephalopathy syndrome (PRES) during induction chemotherapy. This case report aims to describe a complex clinical scenario with severe and atypical presentation in an immunosuppressed host.

## Case Description

A 3-year-old girl newly diagnosed to have a standard risk pre-B ALL with favorable cytogenetics (hyperdiploidy >50 chromosomes, triple hyperdiploid +4, +10, +17) presented on day 10 of induction chemotherapy with febrile neutropenia (Hb: 8.1 gm/dL, WBC: 0.89 × $10^9$ cells/L, platelet count: 16 × $10^9$/L, absolute neutrophil count (ANC): 0.16 × $10^9$ cells /L). There was no past history of COVID-19 infection or contact with COVID-19 infected person. The reverse transcription–polymerase chain reaction (RT-PCR) done for SARS-CoV-2 before admission was negative.

Febrile neutropenia was managed as per institutional protocol and antibiotics were escalated after 48 hours in view of relentless high-grade fever. On day 15 of induction, persistent fever spikes prompted us to do chest imaging. High-resolution computed tomography (HRCT) chest was suggestive of lobulated soft tissue lesion with perifocal haze in left lower lobe suggestive of infective etiology likely fungal. In view of poor general condition and severe neutropenia, she was started on dual therapy with injectable liposomal amphotericin-B and oral voriconazole. Due to classical CT findings, massive COVID outbreak in Delhi (peak of second wave) and limited procedural facilities at that time, bronchoalveolar lavage was deferred.

Subsequently, her tachypnea and hypoxemia worsened. Echocardiogram revealed mild pericardial effusion, myocardial dysfunction with an ejection fraction of 25% and dilated coronaries (LMCA +4.53 SD, LAD +4.02 SD, RCA +2.25 SD). A possibility of MIS-C was entertained. Coronavirus disease (COVID) antibodies tested were strongly positive (total titre-397 IU/L, ref <1). Inflammatory markers were positive including serum ferritin (23,555 ng/mL, ref- 21–274 ng/mL), CRP (104 mg/L, ref >6 mg/L), fibrinogen (2.98 gm/L, ref 2–4 gm/L) and D-dimer (2.7 ug/mL, ref <0.25 ug/mL). She was given intravenous immunoglobulin (IVIG, inotropic support, and steroids were changed from oral prednisolone to injectable methylprednisolone. Diuretics were used to manage associated pulmonary edema.

She had a transient defervescence of fever for 48 hours following which fever spikes recurred. Serum galactomannan, blood culture and CMV PCR were negative. Ejection fraction and coronary artery dilatation showed improvement 72 hours post-immunomodulatory therapy. A differential of fungal infection or hemophagocytic lymphohistiocytosis were entertained. The CT chest was repeated which revealed enlarged necrotic, mediastinal, and left hilar lymph nodes. A cavitatory lesion in the left lower lobe

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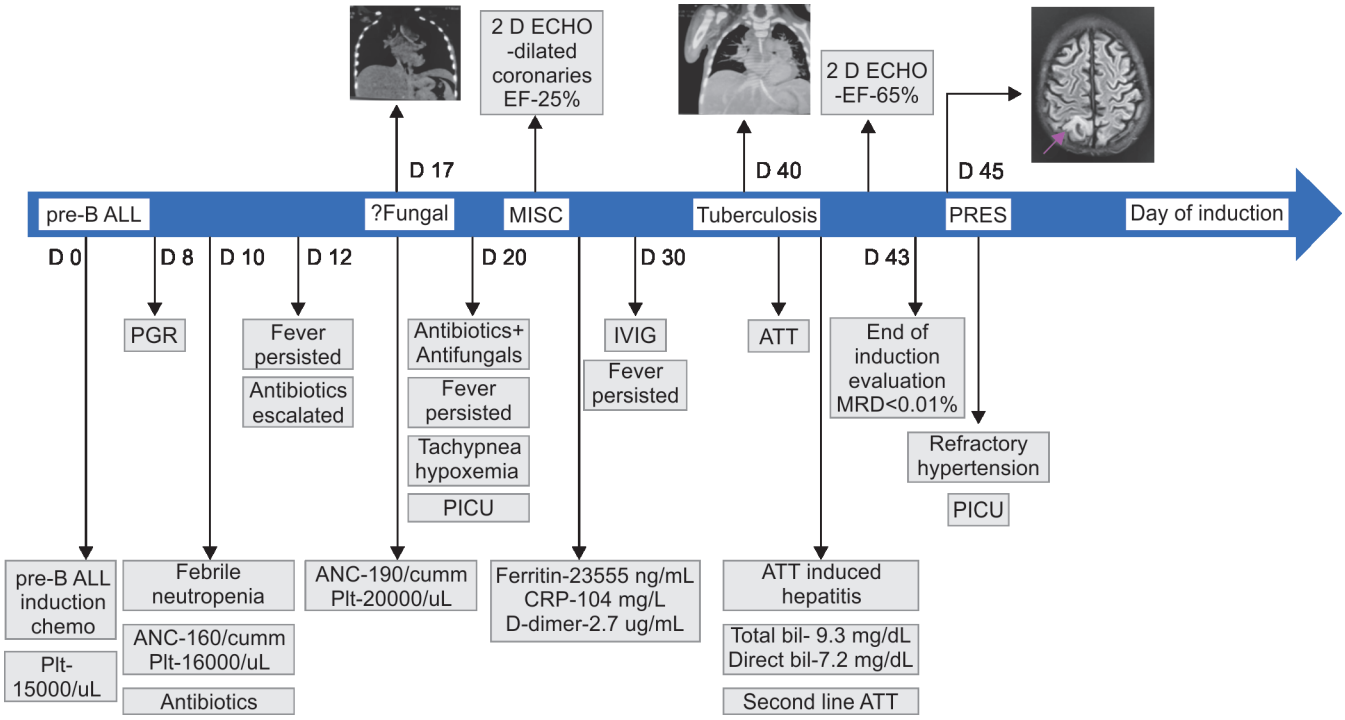


**Fig. 1:** Timeline of events. Days denote the day of induction

and multiple nodular lesions in bilateral lungs were new findings. Broncho alveolar lavage done tested positive for acid-fast bacilli. She was started on antitubercular therapy (ATT) as per revised national TB control program. She developed hyperbilirubinemia (total bilirubin –9.3 mg/dL, direct bilirubin –7.2 mg/dL) and transaminitis (SGOT-413 IU/L, SGPT-390 IU/L). The ATT was changed to second line (isoniazid, pyrazinamide and rifampicin were withheld, levofloxacin, amoxicillin-clavulanate, meropenem added and ethambutol continued) with ursodeoxycholic acid. Ejection fraction improved to 65% and there was normalization of coronaries. She further developed refractory hypertension probably secondary to steroid and MISC and had worsening sensorium with loss of vision. The MRI was suggestive of PRES with no evidence of venous thrombosis or central nervous system (CNS) TB. She needed five antihypertensives to control her blood pressure. Renal, endocrine, and cardiology work up did not reveal a definitive cause of hypertension. With extensive supportive therapy, she stabilized gradually. Antihypertensives were tapered to two drugs, liver function improved, and first line ATT was restarted 3 weeks later (Fig. 1).

She received three-drug induction (steroids, vincristine, and PEG-asparaginase). The end of induction evaluation showed morphological remission on bone marrow and minimal residual disease of <0.01 %. She is being continued on further chemotherapy with ATT.

## Discussion

Generally, MISC in children with cancer is rare owing to their lack of ability to mount immune responses.[1,2] The reported children had an uncomplicated course of MISC and good outcome with immunomodulators.

Although coronary dilation can occur in patient with ALL without a diagnosis of MISC or Kawasaki disease,[3] persistent fever spikes, ongoing pandemic, strong positivity of COVID antibodies suggest a diagnosis of MISC.

Precipitation of PRES by COVID-19 infection has been reported in adults and children with or without hypertension.[4] Also, PRES may occur in these patients due to systemic illness or because of virus-associated necrotizing disseminated acute leukoencephalopathy (VANDAL), possible mechanisms include immune system activation or virus induced endotheliopathy.[5] In our case, the underlying diagnosis of cancer, hypertension, and possibly COVID-19 contributed to this event.

Although TB is a rampant disease in India, its occurrence during ALL therapy in young children is extremely rare despite usage of high doses of steroids and immunosuppressive therapy.[6,7] Tadolini et al. reported concurrence of TB and COVID-19 in 49 adult patients where 14 patients had COVID-19 infection preceding TB. The authors postulated that COVID-19 infection may have boosted the development of active TB. Studies are needed which look at the alterations in immune system post-COVID and confirm this temporal association of TB and COVID.[8] On one hand, social distancing and use of face masks may reduce the transmission of pulmonary Koch's, prolonged T cell depletion post-COVID infection.[9] Usage of steroids, malnutrition, and general debility may cause reactivation of latent TB.

## Conclusion

This case report highlights how MISC can complicate the clinical course of a child with newly diagnosed ALL. The COVID-19, steroids, and MISC may precipitate PRES in presence of contributing factors and COVID-19 associated immunosuppression may predispose to the rare activation of TB. We anticipate facing unique challenges of difficult infections and immune disturbances post a massive second COVID wave that hit India between April 2021 and May

2021. Preparations need to be done for a predicted third wave and awareness of such cases can make pediatric oncologists and intensive care specialists wary of potential complications.

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