Case Report

Severe acute respiratory distress syndrome in a case of congenital tuberculosis with congenital cytomegalovirus infection complicated with secondary hemophagocytic lymphohistiocytosis

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Abstract

Congenital tuberculosis (CT) is rare and is transmitted to the fetus hematogenously through the umbilical vein or by fetal aspiration or ingestion of infected amniotic fluids prior to or during delivery. Congenital cytomegalovirus (cCMV) infections are defined as those infections which are acquired through transplacental entry of organism from maternal blood stream into the fetus or transmitted during passage through the birth canal. We report the case of a 4½-month-old baby presented with fever and respiratory symptoms with hepatosplenomegaly and diagnosed to be a case of CT with cCMV infection further complicated by secondary hemophagocytic lymphohistiocytosis and severe acute respiratory distress syndrome and salvaged by high-frequency oscillatory ventilation, antitubercular drugs, and steroids.

Keywords: Acute respiratory distress syndrome, congenital tuberculosis, cytomegalovirus infection, secondary hemophagocytic lympho histiocytosis

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon heterogeneous group of clinical syndromes characterized by activation and subsequent uncontrolled nonmalignant proliferation of T lymphocytes and macrophages, leading to a hypercytokinemic state that accounts for most of its clinical features such as acute febrile illness, hepatosplenomegaly, and multi-organ dysfunction.[1] HLH may be primary or secondary. Primary/genetic HLH is an autosomal recessive disorder, more prevalent with parental consanguinity. Secondary HLH may occur in severe infections, malignancy, or in rheumatological diseases.[2] Any infection can give rise to secondary infection-associated HLH, used synonymously to some extent as hyperferritinemic sepsis with multiple organ dysfunction by the intensivists.[3]

We report a 4½-month-old infant who was admitted with failure to thrive, microcephaly, fever, pneumonia leading to severe acute respiratory distress syndrome (ARDS), hepatosplenomegaly, bicytopenia, coagulopathy, and ultimately diagnosed as Congenital tuberculosis (CT) with

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cCMV infection complicated with secondary HLH and severe ARDS.

CASE REPORT

A 4½-month-old baby boy was admitted with recurrent fever and cough for 6 weeks, failure to thrive, progressive abdominal distension for 2 weeks, and respiratory distress for the past 5 days. The baby was born out of nonconsanguineous marriage, preterm (35 weeks), normal delivery, birthweight-2.05 kg, cried immediately after delivery, there was no history of neonatal intensive care unit admission. Mother had previous two abortions, both were in first trimester. There was no history of contact with tuberculosis (TB). Baby's immunization was up to date according to national schedule. He had been admitted to two outside hospitals for 2 weeks and treated with broad spectrum intravenous (IV) antibiotics.

On admission, the baby was found to be poorly nourished without any cyanosis, icterus, or clubbing. Respiratory system examination revealed bilateral subcostal retractions, bilateral crepitations. Abdomen was distended, liver − 5 cm enlarged below right costal margin, firm in consistency with sharp margin, nontender. Spleen was 4 cm and firm in consistency. Central nervous system (CNS) examination revealed an irritable baby with microcephaly (head circumference 40 cm, just at 3rd centile) without any meningeal signs or motor deficits. Fundus examination was normal. Investigations showed hemoglobin-8.3 g/dl, total count-14,900/cmm, N66 L32, platelet-4.93 lakhs/cmm, C-reactive protein-147.5 mg/L (normal <5 mg/L), SGPT 116 U/L, and SGOT 86 U/L. Initial chest x-ray revealed bilateral patchy opacities [Figure 1]. He was started on broad spectrum antibiotics (IV meropenem and vancomycin) but the respiratory distress started increasing from day 3 of admission and the baby was transferred to pediatric intensive care unit and the next day he had to be intubated and ventilated due to progressive respiratory failure. Chest X-ray after intubation showed increased bilateral nonhomogeneous opacity [Figure 2] suggestive of ARDS. The baby had been ventilated in pressure control mode with lung protective ventilation strategy. The kid had been further investigated and a TORCH screening had been done .It revealed a positive Immunoglobulin M(IgM) for Cytomegalovirus(CMV) which was later confirmed by a positive blood CMV DNA polymerase chain reaction (PCR) (19,880 copies/ml). Cerebrospinal fluid study and ultrasonography brain was normal. Bronchoalveolar lavage (BAL) gram stain, culture, acid-fast bacilli, and viral PCR were negative but positive for *Mycobacterium tuberculosis* by cartridge-based nucleic acid amplification test (CBNAAT) (rifampicin sensitive) and 4 antitubercular drugs was initiated. In the meantime, the baby deteriorated further by progressive hypoxemic respiratory failure and Chest X ray deteriorated further [Figure 3]. He had been shifted to high-frequency oscillatory ventilation (HFOV) and prone ventilation started. Although the gas exchange had been improved after initiation of HFOV, the baby started having high fever spikes and prolonged bleeding from multiple puncture sites. Investigations showed bicytopenia (total leukocyte count-3100/cmm, N 32, L45, and platelet-46,000/cmm), SGPT-167 U/L, SGOT-127 U/L, total protein-5.6, albumin-2.5, protrombin time-28 s, INR-3, and aPTT-56 s. Considering HLH tests were sent and they showed: Ferritin-18,980 ng/dl,-triglycerides 627 mg/dl, lactate dehydrogenase-2344 IU/dl, and fibrinogen-123 g/L. Blood culture was sterile. IV immunoglobulin (IVIG) (2 g/kg over 2 days) with IV dexamethasone 10 mg/m^2/day was started following bone marrow aspiration which revealed plenty of hemophagocytes. Clinical exome sequencing for

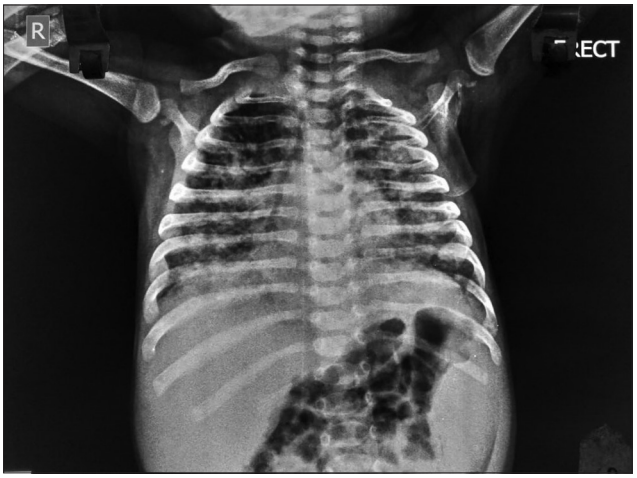

Figure 1: Bilateral patchy opacities in the chest X-ray

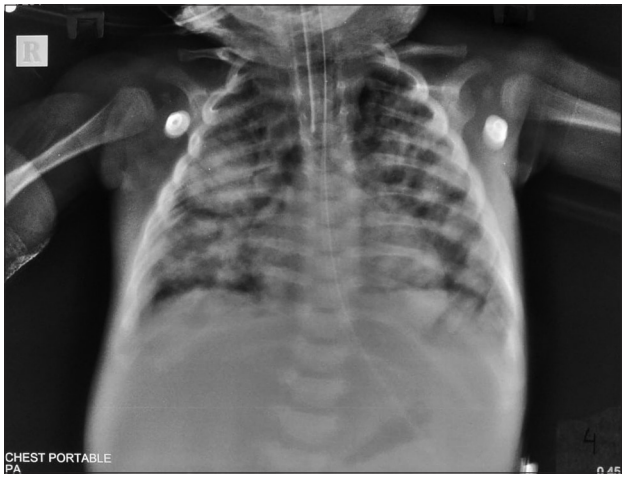

Figure 2: Postintubation chest X-ray, further worsening

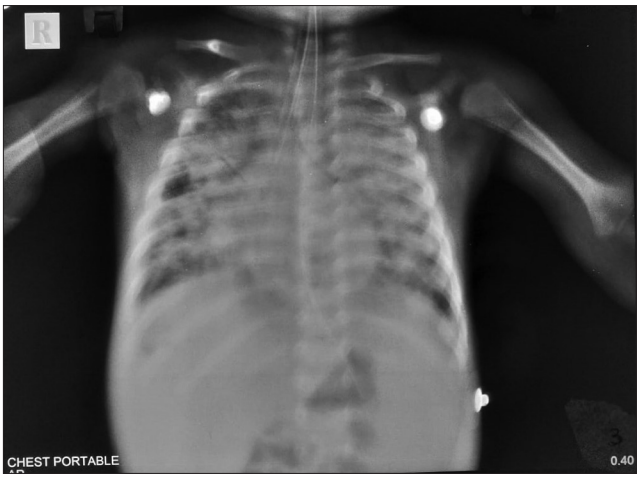

Figure 3: Further deterioration of chest X-ray, almost bilateral white out lungs

genetic HLH was negative. In the meantime parenteral, Koch's screening had been done and the mother was found to be tuberculin skin test positive (15 mm), but chest X-ray and sputum tests were negative. Later, mother's endometrial curettage was done and endometrial biopsy report was suggestive of Koch's. Father's Koch's screening was negative.

Following initiation of dexamethasone and IVIG, the baby became afebrile and blood parameters started improving over the next 72 h. The baby gradually shifted from HFOV to conventional ventilation on day 6 of ventilation and later extubated to noninvasive ventilation on day 9 of ventilation. Dexamethasone was tapered off weekly over 4 weeks and stopped and the baby was discharged on day 34 of admission with 4 antitubercular drugs. Repeat CMV DNA PCR after 2 weeks revealed decreased number of copies, so antiviral agents were not initiated. Over next 8 months of follow–up, the baby was doing well and completed the antitubercular therapy.

DISCUSSION

Our proband was diagnosed with two unrelated congenital infections that were further complicated by secondary HLH and severe ARDS. Both TB and CMV have been implicated as causative organism for infection associated HLH. The presence of prolonged fever with persistent pneumonia and hepatosplenomegaly in spite of treatment with broad spectrum antibiotics raised the suspicion of an unusual causative organism.

Of all the clinical manifestations of TB, CT is rare because genital TB and tubercular endometritis are associated with infertility.[4,5] Despite the high incidence of TB in women of reproductive age, subclinical forms of the disease during pregnancy, coupled with lack of adequate prenatal care in underdeveloped countries, the incidence of CT is estimated at only 2%.[5] Following placental seeding by hematogenous spread of the maternal disease miliary lesions are present in the placenta and spreads to the fetal liver through the blood stream. Perinatal transmission by inhalation or aspiration of infected amniotic fluid during passage through the birth canal results in pulmonary TB in the neonate. Postnatal transmission from open maternal pulmonary TB or other close contacts can result in pulmonary TB in neonates or in early infancy.

Cantwell revised the diagnostic criteria of congenital TB in 1994 that include proven TB lesion in the infant plus any one of the following.[6]

1. Lesion occurring in the 1st week of life
2. A primary hepatic complex
3. Maternal genital tract TB or placental TB
4. Exclusion of postnatal transmission by thorough investigation of contacts.

In our patient, BAL was positive for *M. tuberculosis* by CBNAAT and mothers endometrial biopsy revealed tubercular infection, thus confirming that it was antenatally acquired. Besides this, father's TB work up was negative and no contact had been traced. Hence, we confirmed the diagnosis of CT in our case.

Congenital CMV (cCMV) infection is the most common intrauterine infection though only 10%–15% of these cases are symptomatic at birth. Characteristic symptoms are intrauterine growth retardation, chorioretinitis, prematurity, microcephaly, hepatosplenomegaly, and intracranial calcifications. Early identification of infants with cCMV is important as the optimal treatment window is prior to 1 month of age.[7] Most of the infants are able to abort the infection spontaneously, but those who are severely affected and diagnosed in the 1st month of life are benefitted by the antiviral ganciclovir or valganciclovir.[8] In our index case, it had been detected late at the age of 4½ months. Hence, we followed up the kid with CMV DNA PCR and as viral copies decreased, no antiviral therapy was given. Moreover, IvIg that had been used in our case as an immunotherapy to combat the hyperferritinemia, had a role in disseminated CMV infection.[9]

HLH is a hyper inflammatory disorder resulting from immune dysfunction reflecting either a primary immune abnormality or acquired failure of normal immune homeostasis.[1] Secondary infection-associated HLH has been used interchangeably with hyperferritinemic sepsis

with multiple organ dysfunction syndrome (MODS) by the intensivists.[3] Any infectious agent can give rise to secondary HLH and there are multiple previous case reports of TB and CMV induced HLH.[10-13] In our case, we got two infectious agents *M. tuberculosis* As well as CMV together. However, simultaneous presence of both triggering HLH in a single patient has not been reported yet to the best of our knowledge. It is almost impossible to comment which one of them triggered the event.

ARDS is not uncommon as a manifestation of hyperferritinemic MODS/HLH. We also previously reported a case of TB with HLH and ARDS.[14] Whether this severe ARDS happened due to the lung involvement by the infectious agents (TB and CMV in our case) or as a part of cytokine storm due to hyperferritinemic MODS is a matter of debate.

The treatment of the primary triggering infectious agent along with organ specific supportive therapy is needed in patients of infection-associated HLH/hyperferritinemic sepsis with MODS. Most of the patients need some sort of immunotherapy. HLH 2004 protocol consisting of dexamethasone, etoposide, and cyclosporine with or without CNS-directed therapy should be reserved for genetic HLH cases. There are many studies showing that a low intensive therapy with steroid and IVIG with or without plasma exchange and anakinra are associated with a better outcome than a complete HLH 2004 protocol consisting of cyclosporine and etoposide in secondary HLH/hyperferritinemic MODS.[3,15] We treated the kid with only IVIG and dexamethasone (10 mg/m^2/day) and tapered it over 4 weeks and there was complete recovery without any relapse.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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