A DIAGNOSTIC DILEMMA: WAS THIS DEATH NOT A CASE OF AN INFANT WITH CYTOMEGALOVIRUS INFECTION?

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Abstract

A 3-month-old female infant was referred to a teaching hospital with a 3-day history of fever, fast breathing, cough and 19 hours of yellowish discoloration of sclera. She was deeply jaundiced and febrile, had hepatosplenomegaly, was microcephalic and thrombocytopenic. Child was worked out and treated for bacterial pneumonia, atypical pneumonia, pulmonary tuberculosis, fungal opportunist infection, and heart failure. She was oxygen dependent throughout the 2 months of admission and deteriorated despite all interventions.

Considerations for viral infection was made later into her admission but delayed farther due to financial challenges. Immunoglobins (IgG and IgM) for Cytomegalovirus (CMV) came up positive. Child had hypoxic pneumonia of which CMV is a documented cause in this age group and could have benefitted from empiric ganciclovir cover if clinicians had thought of it.

There is the urgent need for clinicians to widen the differential list especially when response to conventional treatment is poor. Valid National Health Insurance card holders should benefit from a wider range of laboratory services if our aim to decrease infant mortality will materialize.

Key Words: Cytomegalovirus, clinical, misdiagnosis, inappropriate, treatment

Introduction

Cytomegalovirus (CMV) infection like other "TORCHS" infections still remain a significant cause of morbidity and mortality in sub-Saharan Africa. Both congenital and perinatal infections are significant in causing the disease in neonates[1]. Generally, the seroprevalence of CMV is higher in children; with African children reported to have rates in the range of 80% to 100%[1]. Prevalence studies of CMV infection shows that the infection is usually higher in developing countries[2]. CMV IgG seroprevalence among Ghanaian HIV negative blood donors was 77.6% in Accra[3], whilst Kumasi had a higher prevalence of 94.3%[4].

CMV infection can present as severe symptomatic disease among the immunocompromised such as people with HIV, cancer patients and neonates[5]. CMV pneumonia is reported to be the most occurring acute outcome of the infection[1]. Despite the importance of the disease, most diagnosis are made late with a sizeable quota of these diagnoses made at autopsy. This is the case even in developed countries[1]. Diagnosing CMV can be challenging because in symptomatic disease, the presentation can be nonspecific and may involve multiple systems[6]. Diagnosis of CMV can be made by serology, however viral cultures and PCR are preferred[5].

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Conflict of Interest: None Declared

We present in this report the case of a 3-month old infant who was unsuccessfully managed for 2 months on various differential of pneumonia that did not include probable CMV. The diagnosis of CMV pneumonia was made prior to her demise.

Case report

A 3-month-old female infant, weighing 3.2kg, was referred to the Teaching Hospital with a 3-day history of fever, fast breathing, cough and 19 hours of jaundice.

Baby was delivered at full term following an uneventful pregnancy with a birth weight of 2.9kg. Neonatal period was unremarkable.

At age 5-weeks, the infant was managed as an in-patient for 5 days at a peripheral hospital on account of cough. Symptoms had resolved at the time of discharge from the hospital.

Infant was exclusively breastfed up to 6 weeks, at which point mother introduced water. She had received all vaccines as recommended by the Expanded Programme on Immunization for Ghana.

On admission to the ward at the Teaching Hospital, patient was deeply jaundiced and febrile (temperature 38^0C). Spontaneous respiration at 80cpm (high for age), labored with intercostal and lower chest in-drawing. Oxygen saturation on intranasal O_2 was 96% from referral hospital (Patient de-saturated to between 70-80% off oxygen). Bronchial breath sounds with bilateral crackles were heard on auscultation. Heart rate 135bpm, normal heart sounds, capillary refill time <3sec. Palpable liver 5cm and spleen 1cm below the right and left costal margins respectively. Patient was microcephalic (head circumference: 36 cm (< 3^{RD}

centile for age and sex), gained neck control but could not roll on side or to prone position at 3 months.

Total WBC 35.05 x 10^3 /micro/L; Lymphocyte 59.1%; Neutrophil 31.7%; Monocytes 4.8% Platelet: 88 x 10 ^{3}/micro/L; HIV test negative in both mother and child. International normalized ratio (INR) 4.0 (high) Chest X-ray was suggestive of bronchopneumonia (Figure 1)

Working diagnosis

Sepsis secondary to bronchopneumonia with multi organ dysfunction (respiratory and acute hepatic failure) in an infant failing to thrive.

Over a period of 2 months, other diagnoses and treatment were given (table 1) to no avail. Infant kept de-saturating and was on oxygen throughout admission. Temperature remission was not sustained for more than 3 days on any of the modified treatment. In the week patient died, CMV IgG and IgM serology tests came out positive.

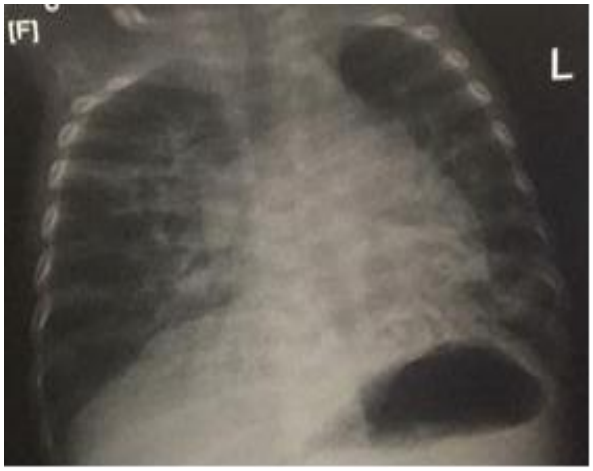

Fig. Chest radiograph showing reticular opacities in both perihilar regions, with silhouetting of a apart of the right cardiac border. Features suggestive of bronchopneumonia**.**

Table1 Diagnosis and treatment timelines for patients

Days into admission	Diagnosis	Treatment/Interventions
0	Sepsis/bronchopneumonia/ acute liver failure with coagulopathy	INO/ IV cefotaxime/gentamicin/IV vitamin k/ syr. lactulose
10	Pulmonary Tuberculosis	Anti-TB therapy with fixed-dose combination HRZ and E)
16	S. aureus Sepsis Atypical pneumonia	Suspension Erythromycin 14day course
19	Cyanotic congenital heart disease	INO
32	GERD with extra-esophageal manifestation	IV/oral omeprazole for total of 21days
37	Atypical pneumonia PJP pneumonia	Bubble CPAP; Oral Cotrimoxazole for total of 21days (interrupted dosing) Oral prednisolone for 7 consecutive days
45	Fungal pneumonia	Oral fluconazole (more affordable) for 14 days
57	Congenital infection (ToRCHeS) CMV Pneumonia	1st dose IV ganciclovir given (died same day)
GERD-Gastroesophageal reflux disease; INO-Intranasal oxygen; IV-Intravenous; S Aureus-Staphylococcus aureus; CPAP-Continuous positive airway pressure		

Discussion

This was a case of a 3-month old female who presented to the ward for almost two months with persistent fever, multi-organ failure and intranasal oxygen dependent unresponsive to all types of antimicrobial. This Infant from the day of admission had signs that were suggestive of CMV if it had been thought through as a differential. Microcephaly, thrombocytopenia, hepatosplenomegaly, deranged INR, and oxygen dependence are all possible in CMV infection[7]. In a 3-month-old, distinguishing between congenital and acquired CMV could be challenging. Low birth weight infants and prematurity increases risk of breastmilk transmission[8]. This infant was born term with birthweight of 2.9 kg. CMV screening is not part of routine antenatal screening in mothers in Ghana and thus the mother's status was unknown prior to delivery. Due

to financial reasons, mother could not be tested on admission. Aside Staphylococcus aureus which was microbiologically confirmed and treated based on sensitivity results, all other diagnosis was presumptive. Chest X-ray showed bilateral infiltrate but was non-specific for any disease. X-ray finding for CMV include characteristic ground glass opacity/consolidation[9]. Patient did not improve on the antibiotic based on the culture results. Being an infant, her immune system was not well developed. Moreover, the long duration of stay on the ward (2 months) and the use of broad-spectrum antibiotics further increased the risk for multiple or nosocomial infections[10]. CMV diagnosis can be made on urine, blood, CSF using PCR. Positive PCR on urine sample in the first 3 weeks of birth confirms congenital CMV[5]. Other tests are Immunoglobulin (IgG and IgM). In our case, both IgG and IgM were positive for infant. The IgM confirm infection in the infant but cannot confirm whether it was acquired or congenital because maternal status was unknown. CMV viral load also confirms infection and is used to determine and monitor treatment progress[11]. Intracranial calcifications are picked by CT scan of the head[12].

Main drugs of choice for CMV are ganciclovir or valgancyclovir[13]. Both drugs have side effects requiring monitoring whiles on treatment. Infants who survive must have hearing, visual and developmental assessment done regularly. In a child with persistent hypoxic pneumonia despite multiple interventions coupled with multi-organ-failure, disseminated CMV should have been a probable diagnosis. Starting ganciclovir empirically could have been life-saving. This case report is emphasizing the need for clinicians to review initial diagnosis when clinical response to presumed diagnosis is poor. Other differentials factoring the age, clinical progression, and epidemiology of diseases within the age bracket is relevant in evidenced-based clinical practice. It is not uncommon for an initial misdiagnosis of clinical presentation especially in an infant. Two months of admission with frequent review, combining features such as microcephaly, fever, jaundice, hepatomegaly, deranged INR, hypoxic pneumonia and poor response on mainly antibiotics, 'TORCHES' infections especially CMV should have featured on the differential list and appropriate interventions boarded.

Conclusion

This infant probably died from CMV Pneumonia which is a treatable disease. A child may present similarly at any facility and lessons from this case could prevent a mortality. The health system should be strengthened so that relevant laboratory tests and medications are available for all children especially valid National Health Insurance Scheme (NHIS) card holders.

Limitations

Financial challenges caused significant delay getting CMV test worked up. Mother could not be investigated and viral load, PCR samples, CT Scan could not be done. Hearing and visual assessment was not done because there was no clinical suspicion to indicate that. Parents refused post-mortem examination.

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