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LETTER TO EDITOR

Of "Cotton Balls" and "Owl's eyes"

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Abstract

Report of a 3-month old girl child who died due to multi-systemic infection of cytomegalovirus (CMV) involving the lungs, liver and kidneys along with pneumocystis jiroveci pneumonia (PJP). The mother of the child tested positive for CMV IgG and HIV with a very low CD4 count (160/ μl). Co-infection of cytomegalovirus and pneumocystis jiroveci always occurs in the setting of immunocompromise. Congenital CMV infection is transmitted through the placenta, especially during the first trimester and causes severe multi-systemic disease whereas perinatal infection is acquired during childbirth/ breastfeeding where the babies have maternal protective antibodies leading to much milder or asymptomatic infection. PJP is more common in infancy and presents as hypoxic pneumonia. CMV causes cyto-nucleomegaly and classic "owl's eye" inclusions on histology while PJP presents with characteristic fluffy "cotton ball" alveolar exudates.

Keywords: cytomegalovirus; pneumocystis jiroveci pneumonia; opportunistic infections, HIV- AIDS, autopsy, histopathology

Dear Editor,

A 3-month old girl presented to the emergency with severe respiratory distress as per history given by mother. On examination, she was unconscious with non-palpable pulse; respiratory and heart sounds were not heard. Pupils were fixed and dilated. Cardio-pulmonary resuscitation was carried out as per advanced life support protocol; however, she could not be revived and patient was declared brought dead. Post-mortem examination was carried in the Department of Forensic Medicine.

Parts of brain, liver, kidney, spleen, pancreas, lungs with hilar structures and heart were received in the Department of Pathology for histopathology examination. Both lungs were heavy and solid to feel with whitish parenchymal patches and dull adherent pleura (FIG. 1A). On microscopic examination, the lungs showed diffuse pink "cotton ball" like alveolar exudates; confirming to the morphology of pneumocystis jiroveci (FIG. 1B). These cup shaped cysts were better highlighted on silver methenamine stain (FIG. 1C). Additionally, few pneumocytes and bronchial epithelial cells showed enlarged nuclei with smudgy basophilic inclusions and perinuclear halo, reminiscent of "owl's eye" appearance (FIG. 1D). These inclusions are highly indicative of cytomegalovirus (CMV) inclusions which were confirmed on immunohistochemistry (IHC) against CMV (FIG. 1D inset). No inspissated secretions were seen in the main bronchi. Grossly, liver parenchyma was pale yellow in colour. It showed predominantly maintained acinar architecture with mild portal inflammation. The hepatocytes showed diffuse non-zonal macrovesicular steatosis. Areas of spotty necrosis were noted. In addition, scattered hepatocytes were enlarged with basophilic nuclear inclusions (FIG. 2A, 2B); confirmed as CMV inclusions on IHC (FIG. 2B, inset). Kidney showed congested glomerular capillary loops with CMV inclusions in the renal tubular epithelium (FIG. 2C, 2D) and glomerular capillaries (FIG. 2D, inset).

Brain showed terminal hypoxic changes. Spleen was mildly congested; heart was largely unremarkable while pancreas showed autolytic changes. Based on the autopsy findings, a final diagnosis of PJP pneumonia along with CMV hepatitis, CMV pneumonitis and CMV infection of

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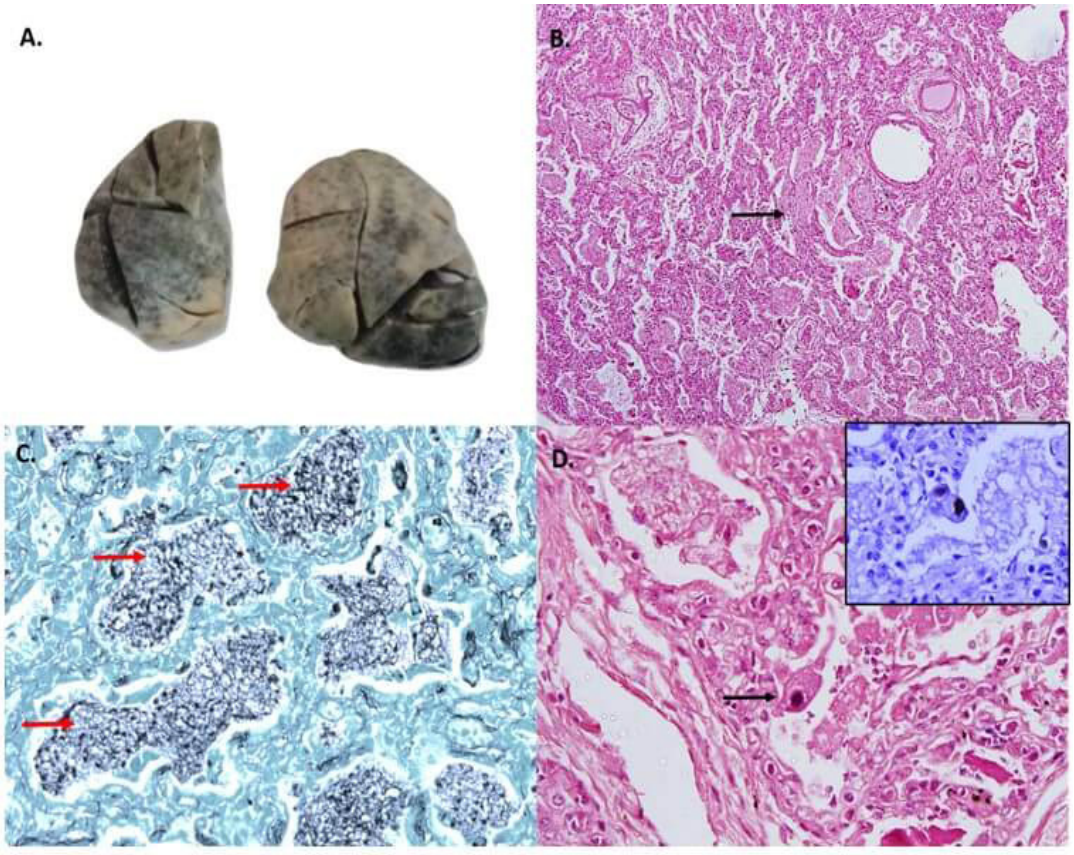

FIG. 1: (A) Gross picture of both lungs showing whitish parenchymal patches and dull adherent pleura. (B) On histology, lungs show diffuse fluffy cotton ball like exudates within the alveolar spaces (black arrow) {Haematoxylin and Eosin (HE), 100x}. (C) Alveolar exudates of PJP highlighted on Grocotts' silver methenamine stain (red arrows) (GMS, 400x). (D) Interstitial pneumocyte showing classic "owl eye" inclusion of CMV (black arrow) (HE, 400x); immunoreactivity for CMV antibody in an infected pneumocyte (inset) (CMV IHC, 400x).

kidney was given. HIV testing advised for parents. The mother gave history of frequent episodes of respiratory infections and diarrhoea for which she sought local treatment. Both parents tested positive for HIV, with a very low CD 4 count of 160/ μl in the mother and 432/ μl in the father. She was also found to have high serum IgG antibodies to CMV and subsequently put on highly active antiretroviral therapy.

CMV is a beta herpes virus with sero-prevalence of more than 80% in HIV infected individuals.[1] CMV causes suppression of the T lymphocyte function.[2] Thus immune compromised individuals are more prone to severe CMV disease manifestations or end organ damage (EOD). All types of EOD including retinitis, pneumonitis, hepatitis, encephalitis and colitis are AIDS defining conditions.[2] CMV also enhances HIV progression and transmission by undefined mechanisms, thereby increasing mortality. Congenital CMV infection, which occurs in 0.2 to 1% of live births worldwide, results from trans-placental acquisition of maternal infection.[3] Clinically, apparent disease in the neonate is much more likely to occur after primary maternal exposure. Perinatal CMV infection is acquired by exposure to infected cervical secretions or breast milk where maternal antibodies are thought to be protective. Most exposed term infants are therefore asymptomatic. In this case, baby was full term, not breast fed and showed severe multi-systemic involvement by CMV; it is likely that she had congenital CMV infection. Diagnosis in the neonate is made by viral detection in body fluids via PCR, culture, or antigen testing (pp65 antigen) within the first 3 weeks of life.[4] CMV infects endothelial cells, fibroblasts as well as epithelial cells. On microscopy, CMV causes cytonucleomegaly with the classic smudgy basophilic inclusions having perinuclear halo; the "owl's

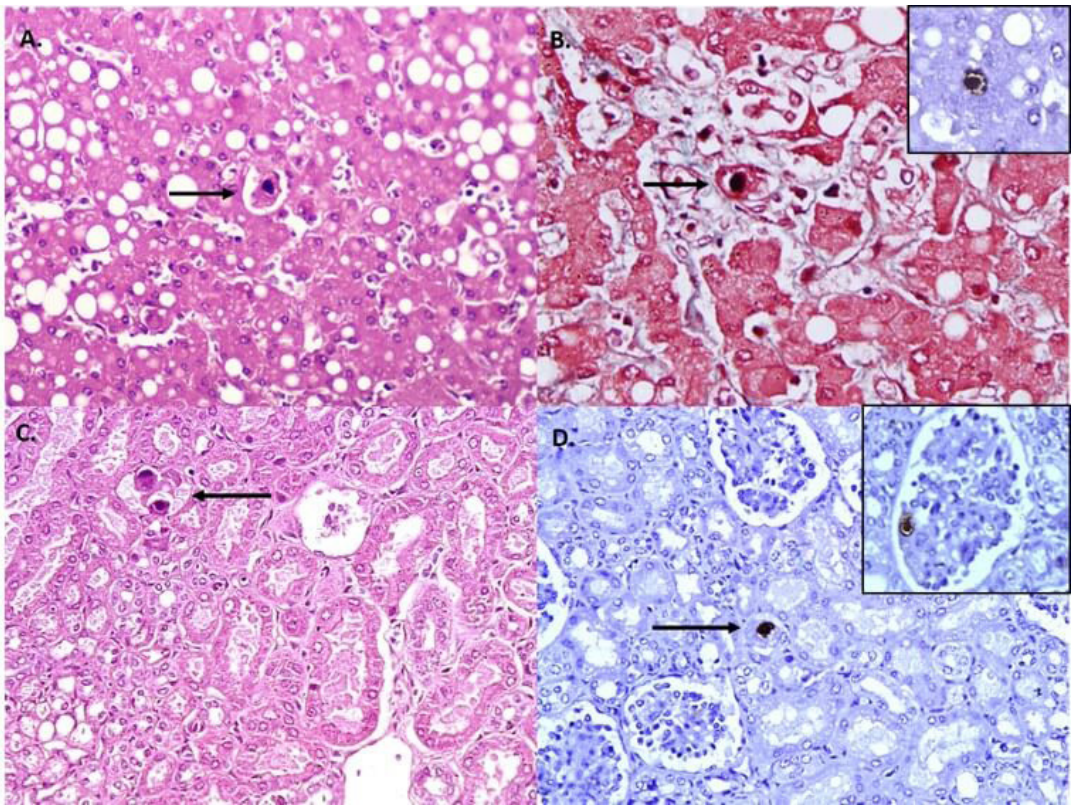

FIG. 2: (A) A hepatocyte showing CMV inclusion (black arrow) while surrounding parenchyma shows diffuse macrovesicular steatosis (HE, 200x). (B) Hepatocytic nucleus with "owl" eye inclusion with surrounding hepatocytic dropout (Masson trichrome, 400x). (C) Renal proximal tubular epithelial cells showing CMV inclusions (HE, 200x). (D) Immunoreactivity for CMV antibody in an infected renal tubular epithelial cell (CMV IHC, 200x) and glomerular endothelial cell (inset, CMV IHC, 400x)

eye" inclusions.

Pneumocystis jiroveci (PJP) pneumonia is very rare and raises strong concern of immunodeficiency. Therefore, co-infection with CMV and pneumocystis jiroveci almost always occurs in setting of immune compromise.[5] PJP can occur at any age but is more common in infancy and is often the presenting manifestation of infants less than six months of age, irrespective of CD4 counts.[5] Clinically, it presents as hypoxic pneumonia with 'ground glass' reticulo-nodular opacities on chest radiograph. PJP is diagnosed by identification of cysts in bronchioalveolar lavage, sputum or lung biopsy sample.[6] Collections of fungal cysts form alveolar casts giving a foamy appearance which can be highlighted on Grocotts methenamine silver stain.[6] The case fatality rate of PJP is 100% if timely treatment is not administered.[5] With the advent of antiretroviral therapy, the number of HIV infected patients presenting with opportunistic infections has considerably reduced. However, in developing countries people belonging to low socio-economic strata are still susceptible to develop HIV associated co-infections due to lack of awareness and early treatment.

Authors' contribution: SM has written and worked up the case and taken the gross and microphotographs. AG and RKS played a role in critical review of the manuscript.

Conflict of interest: The authors declare no conflict of interests.

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