

Cystic Fibrosis with Cytomegalovirus Induced Pneumonitis Case Series

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Abstract

Cystic fibrosis (CF) is a multisystem disease characterized by recurrent respiratory tract infections and progressive respiratory failure. It remains one of the most common life-threatening autosomal recessive condition in children .In cystic fibrosis (CF) it has been found that an incidence of up to five times of Viral Respiratory Infection (VRI) per patient-year. Viral infections in this population are associated with increased respiratory symptoms and disease progression. Up to 64% of pulmonary exacerbations in pediatric CF populations are associated with respiratory viruses, yet the literature on VRI in adults with CF is sparse. Cytomegalovirus (CMV) is a DNA virus and a member of the herpes family of viruses, which includes herpes simplex virus, Epstein–Barr virus (EBV) and varicella–zoster virus. Like these other viruses, once primary infection has occurred, CMV establishes itself in the host in a latent form with periodic episodes of reactivation occurring throughout life. CMV is a common infection with most individuals acquiring infection at some time. Both primary and no primary infections are associated with viral shedding in urine, saliva, semen, cervical secretions, breast milk and other body fluids. In healthy individuals, symptoms of CMV infection are often mild and nonspecific, or absent altogether, and rarely cause serious illness. However, CMV infection can be life threatening to immune compromised individuals, such as those with advanced HIV infection, transplant recipients or very premature infants.

CMV infection is an uncommon cause of respiratory complications in immune competent patients, although CMV pneumonia is being recognized more frequently in immune competent adults and children. It is a leading cause of morbidity and mortality in immune suppressed patients as well as very premature and congenitally infected infants. In lung transplant recipients, it is associated with acute syndromes and graft rejection. There are no available data on the prevalence and impact of CMV in patients with CF. We describe four cases of primary CMV infection causing significant pulmonary exacerbation in Pediatric with CF. The presentation in last three cases out of four reported here was remarkably similar, although in case one seroconversion had not yet occurred and was diagnosed after failure to respond to broad-spectrum antibiotics and sweat chloride test. The characteristic features were lymphocytosis, intermittent fever unresponsive to intravenous (I.V.) antibiotics and a persistent weight loss but last three declines in lung function. In our unit, viral throat swabs are routinely taken in all patients presenting with acute pulmonary exacerbations and lymphocytosis is not associated with respiratory viral infections such as respiratory syncytial virus, influenza and par influenza. The diagnosis of primary CMV infection was based on the presence of CMV IgM and CMV PCR. Last two patients had significant viral loads and low CMV IgG avidity. The first three patients with the highest lymphocyte counts were treated with valganciclovir, and showed significant clinical improvement last three patients return of lung function back to baseline. Currently, there is little evidence using ganciclovir or valganciclovir for treatment of severe CMV infection in immunocompetent patients. In summary, we have demonstrated that respiratory viruses especially CMV Viruses are common pathogens in Pediatric with CF and are strongly linked to pulmonary exacerbations. So we should have ultimately led to effective new treatments to prevent virus-induced exacerbations in patients with CF.

Keywords: Cystic Fibrosis, Cytomegalovirus, Pneumonitis.

INTRODUCTION

Cystic Fibrosis (CF) is a recessive disease involving an autosomal gene, the Cystic Fibrosis Trans-membrane Conductance Regulator (CFTR) gene located at 7q31.2, (Fig.-1) which regulates the activity of chloride and sodium channels at the surface of the epithelium cell [1-3]. The mode of inheritance of CF is 25% affected, 25% normal and 50% carrier (Fig.-2). This disease affects the cells that produce mucus and sweat in multiple organs, being the lung the most severely affected and responsible for 90% of the deaths in patients with CF [4].

Cystic fibrosis (CF) is a multisystem disease characterized by recurrent respiratory tract infections and progressive respiratory failure. Viral infections in this population are associated with increased respiratory symptoms and disease progression. Up to 64% of pulmonary exacerbations in pediatric CF populations are associated with respiratory viruses, yet the literature on VRI in adults with CF is sparse.

[5-6]. Recent studies have highlighted the association between respiratory viral frequency of pulmonary exacerbations, increase antibiotic usage also [6].

Cytomegalovirus (CMV) is a DNA virus and a member of the herpes family of viruses, which includes herpes simplex virus, Epstein-Barr virus (EBV) and varicella-zoster virus. Like these other viruses, once primary infection has occurred, CMV establishes itself in the host in a latent form with periodic episodes of reactivation occurring throughout life. CMV is a common infection with most individuals acquiring infection at some time. Both primary and no primary infections are associated with viral shedding in urine, saliva, semen, cervical secretions, breast milk and other body fluids. In healthy individuals, symptoms of CMV infection are often mild and nonspecific, or absent altogether, and rarely cause serious illness. However, CMV infection can be life threatening to immune compromised individuals, such as those with advanced HIV infection, transplant recipients or very premature infants.

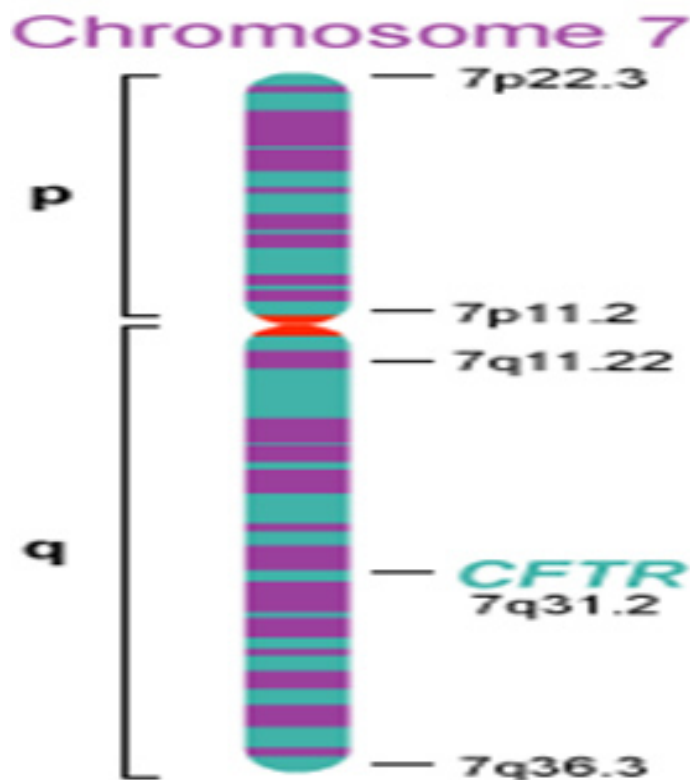


Fig 1. Cystic Fibrosis Gene located on Chromosome no 7, in long arm 7q31.2 position.

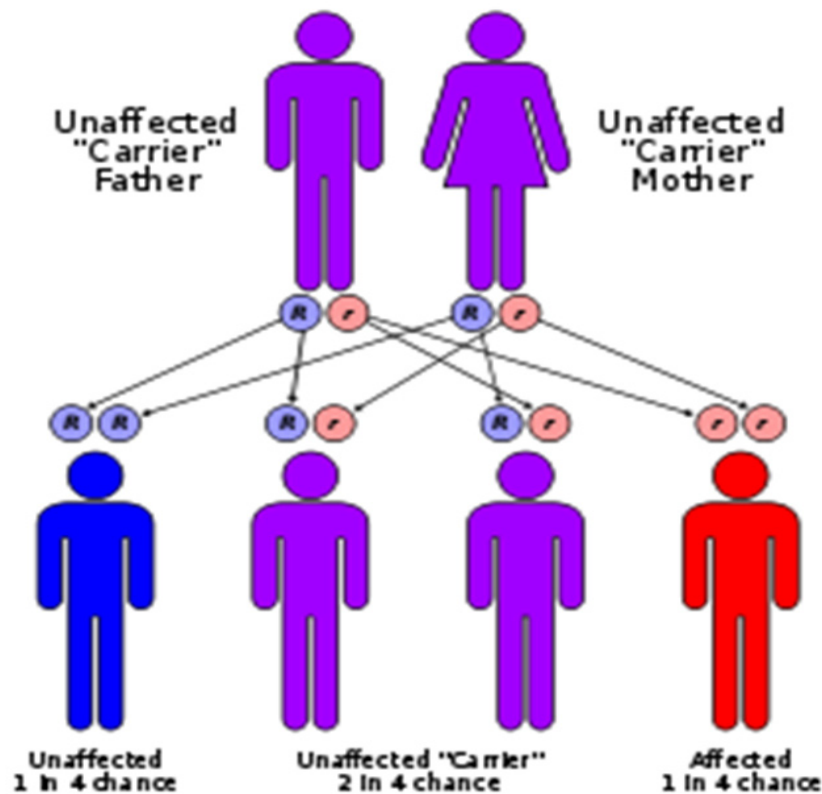


Fig 2. Mode of Inheritance of CF. 25% affected, 25% normal and 50% carrier.

CASE STUDIES

We describe four cases of primary CMV infection causing significant pulmonary exacerbation in Pediatric with CF. First case A , 6 months old boy, 3rd issue of consanguineous parents, immunized as per Expanded Programmed on Immunization (EPI) schedule, admitted with the complaints of low grade intermittent fever, cough and respiratory distress for 1 month . He had history of (H/O) repeated Respiratory Tract Infection (RTI) since 20 day of age, runny nose, wheezing and passage of loose greasy stool. Cough had no diurnal variation. No h/o exhaustion during feeding, overcrowding, contact with TB patient .Family h/o allergy present. For these complaints, he was treated by antibiotics and nebulization with salbutamol and budesonide but was not improved. He was delivered by LUCS at term, passed urine and meconium within 24 hour & perinatal period was uneventful. He was on exclusive breast feeding (EBF). On examination, he was ill looking, mildly pale, dyspneic with flaring of alar nasi and head nodding present. Clubbing, cyanosis, jaundice absent. He was tachypneic (R/R-70 /min), pulse 128 /min, temperature 101 F, Bacillus Calmetree Gurein (BCG) mark present. His weight was 5.1 kg lies

at 10th centile, length was 58cm lies between 10th and 25th centile, Bagginess on both gluteal region (Fig.-3). Chest movement was bilaterally symmetrical. Chest in drawing present. Trachea centrally placed, apex beat not shifted. Breath sound vesicular with prolong expiration, wheeze present. Crackles were audible on right lung fields. Liver is palpable about 3cm from right costal margin with sharp border, smooth surface and firm in consistency , upper border of liver dullness in 5th Inter Costal Space (ICS). Other system revealed no abnormality, Full blood count showed - Hb%-11.9 g/dl, Total count of White Blood Cell- 9,900 /cumm, lymphocyte 70%, platelet count: 400,000 /cumm ESR - 19 mm in 1st hour, Capillary blood Glucose- 5.7 mmol/l, Serum. Electrolyte- Na- 137 mmol/l, K-4.9 mmol/l Cl- 106 mmol/l, Arterial Blood Gases (ABG) - PH- 7.343 , PCO₂- 38.4 mmol/l, PO₂- 79 mmol/l, HCO₃- 22 mmol/l, Serum Creatinine - 0.3 mg/dl, Urine Routine- examination- Normal. Faecal fat estimation was negative but Sweat Chloride test was positive on two occasions. Chest radiography showed perihilar haziness with infiltration(Fig.-5).

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Alanine transaminase (ALT) - 46 mg/dl, Serum Ammonia-30, S.Lactate-1.8, and Urinary Ketone -not detected Cytomegalo Virus (CMV) Ig G-43.5 IU/ml, CMV Ig M- 67.8AU/ml, Repeat ABG showed- PH- 7.46, PO2- 62 PCO2- 30 HCO3 - 23 mmol Respiratory

alkalosis, Type 1 respiratory failure. The patient had significant improvement with three weeks course of oral valganciclovir. Continuous Positive Air way Pressure (CPAP) was also needed at the end part of management.



Fig 3. *Bagginess of gluteal region*



Fig 4



Fig 5. Chest X-Ray reveals haziness on Right parahilar region.

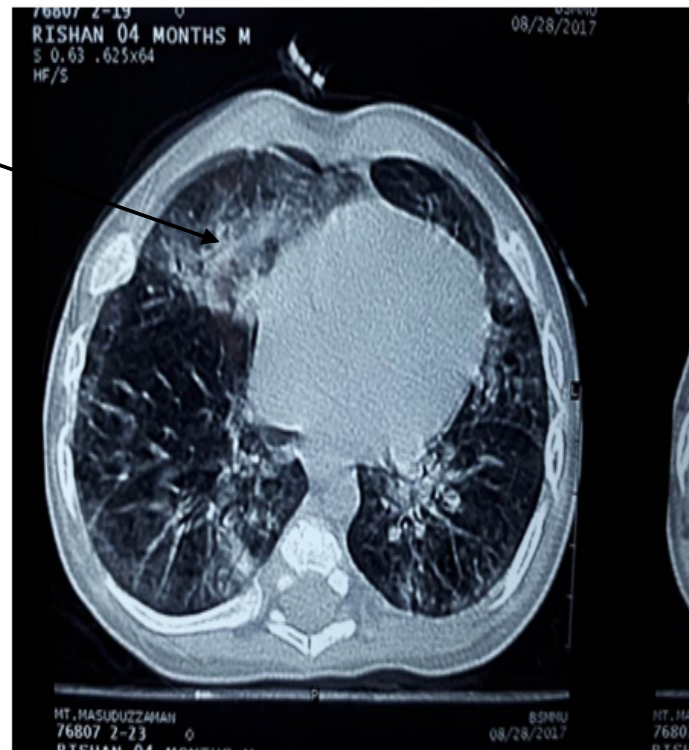


Fig 6

HRCT

Increased attenuated area with ground glass opacity and calcification noted in all segment

of both lungs. Dilated bronchiole with mucous plugging. Bilateral pulmonary inflammatory lesion.(Fig.-6, 7, 8).

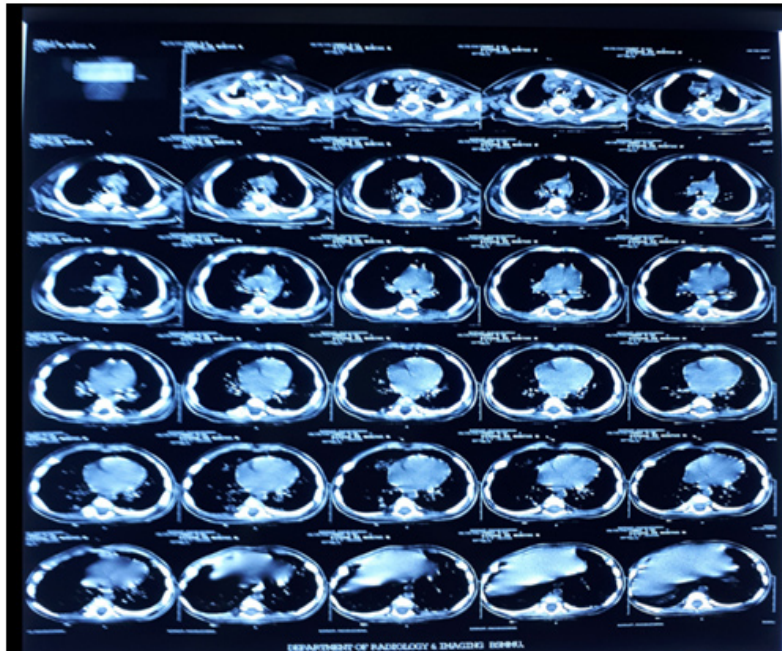


Fig 7

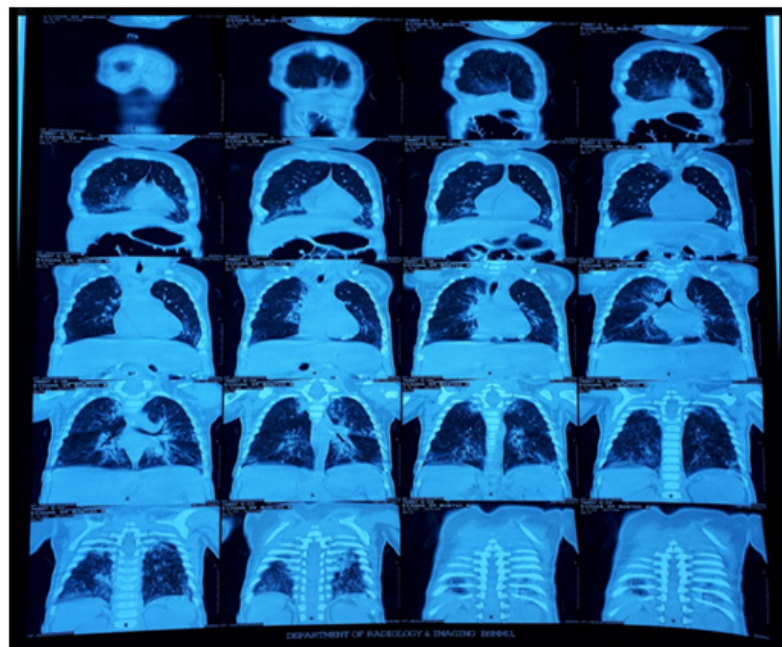


Fig 8. (CT Chest)

The second case involved a 10-year-old girl with CF who presented with a 1-week history of dyspnea and productive cough with green sputum. She complained of generalized headaches, nausea, vomiting and loose stools. . There was no history of sore throat, rash or fever. Lung function had deteriorated, full blood count (FBC) was unremarkable and C-reactive protein (CRP) was elevated at 45 mg·L⁻¹. A viral throat swab was negative, as was the Epstein- Barr- Virus mono spot. A high-resolution computed tomography scan

demonstrated widespread bronchiectasis with no focal consolidation. (Fig.-9). Other investigations included a negative CMV PCR and blood cultures. Despite broad-spectrum antibiotics, she remained dyspnoeic, had persistent high, fluctuating temperatures and lung function remained unchanged. Sputum cultures were positive for *Pseudomonas aeruginosa*, which was fully sensitive to her antibiotic regimen, CRP remained elevated at 45 mg·L⁻¹ and she developed an acute lymphocytosis of 11.53×10⁹ per L.A transt

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horacic echocardiography demonstrated moderately impaired left ventricular systolic function. A CMV IgM and IgG antibody test was positive. A diagnosis of acute CMV infection was made and she was started on a 3-week course of valganciclovir. There was a dramatic improvement in lung function and weight, and both fever and lymphocytosis resolved. A follow-up echocardiography demonstrated mildly hypokinetic basal-to-midseptal contraction.

The third case occurred in a 15-year-old girl with CF. She presented with a 3-week history of productive cough, chest tightness, spiking temperatures, fatigue, and a blanching maculopapular rash affecting her upper limbs and trunk. There was no lymphadenopathy or organomegaly. Forced expiratory volume in 1 s (FEV1) was significantly reduced at 56% predicted from a baseline of 70–80% predicted. Blood lymphocyte count and CRP were elevated at 16.98×10^9 per L and $44 \text{ mg} \cdot \text{L}^{-1}$, respectively. A chest radiograph showed patchy consolidation in the right mid- and lower zones (Fig. 11), and blood cultures were negative. CMV IgM and IgG antibody test was positive with a PCR viral load of $23\,120 \text{ copies} \cdot \text{mL}^{-1}$. A viral throat swab was negative, as was the EBV monospot. However, EBV PCR was positive with $961 \text{ copies} \cdot \text{mL}^{-1}$. After 2 weeks of intravenous antibiotics she remained unchanged, and lung function remained low. Following a 3-week course of valganciclovir, she made a full recovery and an FEV1 of 77% predicted. The CMV PCR titre fell to $1413 \text{ copies} \cdot \text{mL}^{-1}$ and lymphocytosis resolved.

The final case involved a 12-year-old girl with CF who presented with high spiking temperatures, productive cough and general malaise. Sputum was chronically colonized with *P. aeruginosa*. On admission, FBC was unremarkable (white cell count 9.17×10^9 per L, lymphocyte count 1.44×10^9 per L), CRP was elevated at $102 \text{ mg} \cdot \text{L}^{-1}$ and there was patchy consolidation on chest radiography. She had a 2-kg weight loss and her FEV1 had dropped from 80% to 64% predicted. Viral throat swab PCR was positive for parainfluenza type 4. Despite a week of i.v. Colistin and oral clarithromycin, she continued to experience spikes in body temperature. Multiple peripheral and port cultures were negative as was a repeat viral throat swab but a repeat FBC showed acute lymphocytosis (5.82×10^9 per L). In view of ongoing temperatures and lymphocytosis, a CMV/EBV PCR screen was performed. CMV PCR was positive whilst EBV and adenovirus were not detected. CMV IgM was positive and CMV IgG avidity was low, confirming active primary CMV infection. After 4 weeks of i.v. antibiotics, she made a slow recovery with symptom resolution. Her FEV1 increasing after 4 weeks and to 74% predicted lymphocytosis resolved, and a repeat CMV PCR fell to $2432 \text{ copies} \cdot \text{mL}^{-1}$. CT Chest showed Bronchiectatic changes (Fig.-10). All the cases CT Chest showed Bronchiectatic changes except case 1 which also showed increased attenuated area with ground glass opacity and calcification noted in all segment of both lungs which is very much suggestive of CMV infection. Dilated bronchiole with mucous plugging. Bilateral pulmonary inflammatory lesion.

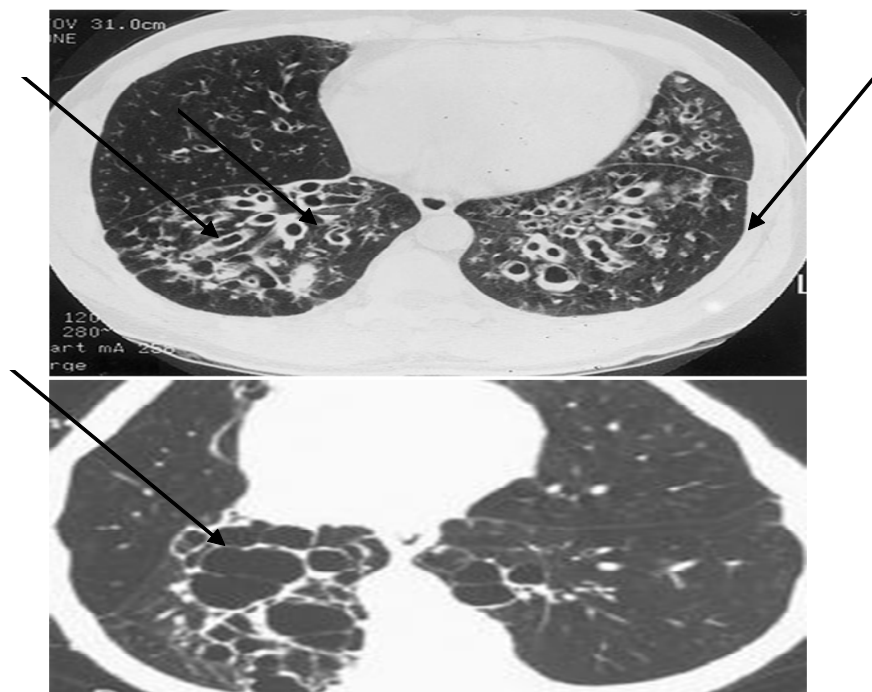


Fig 9. Bronchiectatic-changes zFF

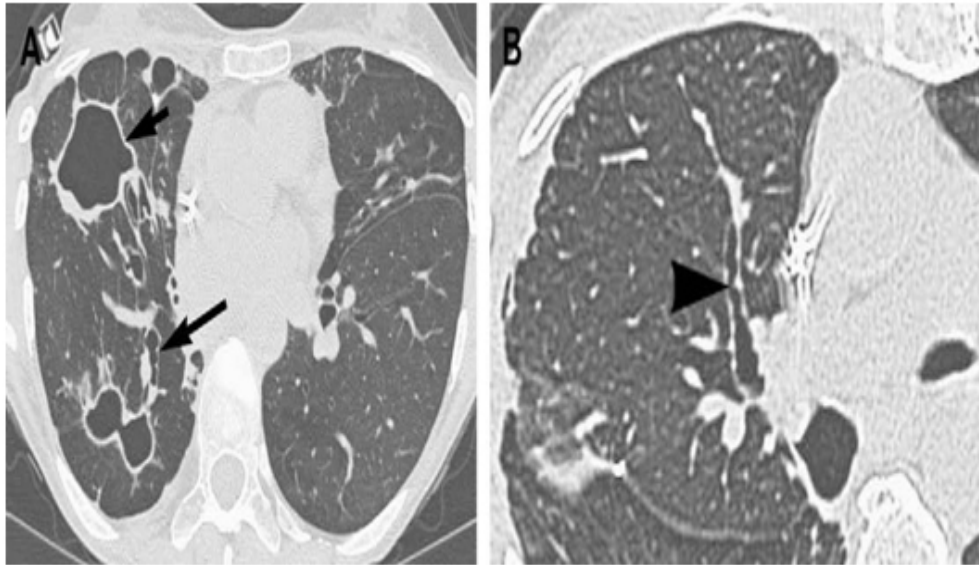


Fig 10. (Bronchiectatic Changes)

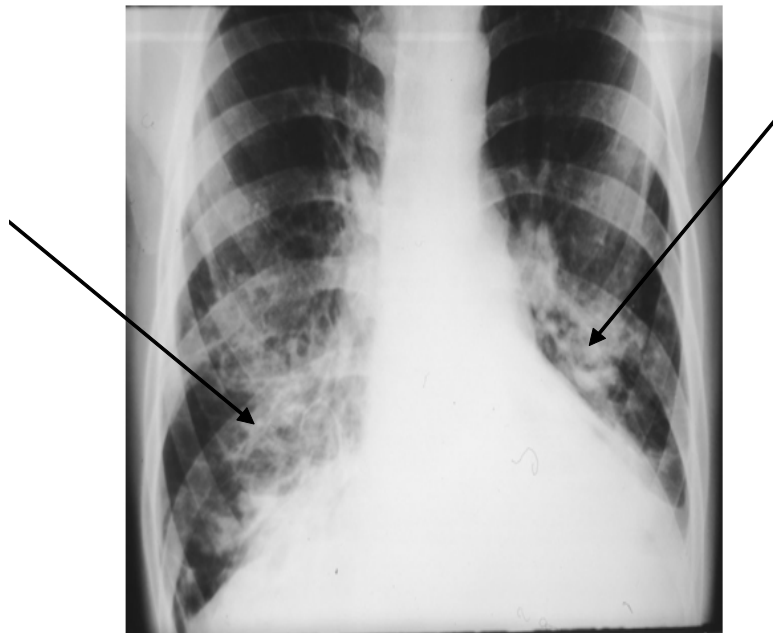


Fig 11. (Bronchiectatic changes)

DISCUSSION

CF a multisystem disease Autosomal recessive inheritance .The name CF refers to the characteristic scaring (fibrosis) and cyst formation within the pancreas. Cause: mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene Chromosome 7, Codes for a c-AMP regulated chloride channel

Most common “life-shortening” recessive genetic disease in Caucasians .Prevalence of Cystic Fibrosis is 1:3,500 newborns in the US, 1 in 10,500 Native

Americans, 1 in 11,500 Hispanics, 1 in 14,000 to 17,000 African Americans, and 1 in 25,500 Asians.

The relationship between pulmonary exacerbations, respiratory viruses and decline in lung function warrants close analysis. Most pediatric CF studies have found accelerated lung function decline in patients with more frequent viral infections. We found that respiratory viruses double the risk of Pulmonary infection/exaggeration(PE) and, separately, that the incidence of PEx is linked to an increased rate of FEV1 deterioration [5-6].

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Cystic fibrosis is very rare in Bangladesh but about 30,000 people affected in US, >10 million people are carriers of mutant CFTR gene, 80% cases diagnosed by age 3 yr.

Cystic Fibrosis (CF) is a genetic condition with high prevalence among Caucasian populations with an incidence of 1:2500 live births. One in 25 persons is asymptomatic carriers. CF can be diagnosed at birth for early medical and nutrition intervention that can lead to improved outcomes [7,8]. And although most people with classic CF will be diagnosed through newborn screening or symptoms in early childhood, there are atypical forms of CF that will only be recognized in adults. The diagnosis in the first year of life is typically accompanied of meconium ileus, failure to thrive, pulmonary infections, diarrhea, and steatorrhea. In adults, patients usually present respiratory symptoms or male infertility due to Congenital Bilateral Absence of the Vas Deferens (CBAVD) [9].

Our three out of 4 patients have manifested chronic productive cough and recurrent pneumonia since their infancy, and *P. aeruginosa* was isolated from their sputum specimens. These findings are consistent with the previous reports about CF, in which acute or persistent respiratory symptoms are the most common clinical manifestations and *P. aeruginosa* is the most commonly identified pathogen from the respiratory tract cultures (10).

Although gastrointestinal symptoms were not apparent in the first and second patient, in contrast to the third and fourth patient, her respiratory symptoms and signs were strongly suggestive of CF. Their diagnosis was confirmed as late as at the age of 9, 10, 12 years respectably and for the first patient in 6 month of age, although the median age of the diagnosis of CF is 6 months (10). Diagnosis of CF was delayed because reliable sweat test was not available in Bangladesh so far.

Since the sweat electrolytes abnormalities in CF patients were first described by di Sant'Agnese (11), the sweat test is considered as the most valuable diagnostic procedure. Despite its importance in the correct diagnosis of CF, false sweat test results can occur by several factors such as unreliable methods, technical errors of evaporation and contamination, the errors in instrument calibration, and the errors in interpretation (12). Therefore, a quantitative

pilocarpine iontophoresis sweat test has been widely used as a reliable standard method, and CF is diagnosed by an increased chloride concentration of more than 60 mM/L on two or more occasions. Our cases were diagnosed by the standardized pilocarpine iontophoresis recommended by NCCLS. Although some laboratories measure sweats sodium concentration, we do not expect additional diagnostic information (13). Many clinical laboratories use chloride meter for the sweat chloride test, and the mercurimetric titration method is only performed in 8% of U.S.A. clinical laboratories, which requires manual procedure (14). The latter can be a good alternative when the chloridometer is not available.

CMV infection is an uncommon cause of respiratory complications in immunocompetent patients, although CMV pneumonia is being recognized more frequently in immune competent adults and children [15–18]. It is a leading cause of morbidity and mortality in immunosuppressed patients as well as very premature and congenitally infected infants. In lung transplant recipients, it is associated with acute syndromes and graft rejection [19, 20]. There are no available data on the prevalence and impact of CMV in patients with CF. A small study by ONG et al. [21], investigating serological evidence of CMV and respiratory viral infections in 36 patients with CF, reported a single case of CMV seroconversion in 11 patients with viral or mycoplasma infections. A further two cases of presumed CMV have been reported in abstract form [22]. Both cases were complicated by allergic bronchopulmonary aspergillosis and despite clinical features being consistent with CMV infection, there was no reference to CMV serology or PCR diagnosis.

The presentation in the three cases reported here was remarkably similar, although in case one seroconversion had not yet occurred and was only diagnosed after failure to respond to broad-spectrum antibiotics and sweat chloride test. The characteristic features were lymphocytosis, intermittent fever unresponsive to i.v. antibiotics and a persistent weight loss but other three declines in lung function. In our unit, viral throat swabs are routinely taken in all patients presenting with acute pulmonary exacerbations and lymphocytosis is not associated with respiratory viral infections such as respiratory syncytial virus, influenza and par influenza. We have seen similar case presentation in a patient with acute

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EBV infection although this was associated with significant lymphadenopathy. The diagnosis of primary CMV infection was based on the presence of CMV IgM and CMV PCR. Our last two patients had significant viral loads and low CMV IgG avidity. The first three patients with the highest lymphocyte counts were treated with valganciclovir, and showed significant clinical improvement and return of lung function back to baseline. Currently, there is little evidence using ganciclovir or valganciclovir for treatment of severe CMV infection in immunocompetent patients.

CMV is an unusual cause of pulmonary exacerbation in immunocompetent individuals with CF. It can present acutely and is heralded by lymphocytosis. Recognizing the symptoms and clinical features of the infection is important to ensure appropriate management. Further studies are needed to assess the burden of CMV disease in CF, reactivation of latent infection or re-infection, and to investigate the safety and efficacy of antiviral therapy in the immunocompetent children.

In summary, we have demonstrated that respiratory viruses especially CMV Viruses are common pathogens in Pediatric with CF and are strongly linked to pulmonary exacerbations. Further research needs to be directed towards understanding the pathophysiology of these infections and virus bacteria interactions within the CF lung. So we should have ultimately led to effective new treatments to prevent virus-induced exacerbations in patients with CF.

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