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Bronchiolitis Obliterans- A Case Report

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Abstract

Bronchiolitis obliterans (BO) is a rare form of chronic obstructive lung disease that follows an insult to the lower respiratory tract characterized by inflammation and fibrosis of the terminal and respiratory bronchioles that lead to narrowing and/or complete obliteration of the airway lumen. Despite diverse etiology, similarity of pathological findings would suggest that BO is the final common pathway of response to different injuries to the lower respiratory tract. The characteristic symptom-complex includes dyspnea, chronic cough, sputum production and wheezing. Although histopathology remains the gold standard for diagnosis, high resolution computed tomographic scan is almost conclusive and replaces the invasive procedure in children. We report a case of BO in a seventeen months old child occurring after an episode lower respiratory tract infection requiring prolonged ventilation and subsequent development of subcutaneous emphysema, pneumomediastinum, hypertension and transient immunosuppression as complications. Our patient had a protracted clinical course with good response to corticosteroids, azithromycin and hydroxychloroquine.

Keywords: *Bronchiolitis obliterans (BO), children, ventilation*

Introduction

Bronchiolitis obliterans (BO) is an uncommon and severe form of chronic obstructive lung disease in children that results from an insult to the lower respiratory tract. In children, BO is frequently preceded by respiratory tract infections by adenovirus, influenza, respiratory syncytial virus (RSV), parainfluenza, measles or mycoplasma pneumoniae. Other causes are collagen vascular disease, Steven-Johnson Syndrome, toxic fume inhalation, chronic hypersensitivity pneumonitis, drugs (such as penicillamine or cocaine) and post transplantation.[1] Post infectious bronchiolitis obliterans may be more common in the southern hemisphere and among persons of Asian descent.[2] With the exception of specialized centers where large numbers of pediatric transplant have performed, post infectious BO is generally the most common form of BO in children. Despite diverse etiology, similarity of pathological findings would suggest that BO is the final common pathway of response to different injuries to the lower respiratory tract characterized by partial or complete occlusion of the lumens of terminal and respiratory bronchioles by inflammatory and fibrous tissue.[3]

Case Report

A 17-month-old girl, only issue of a non-consanguineous parents presented to us with the history of cough and respiratory distress for last 1 year. Her birth history was uneventful (LUCS, Term, Average BW-3.25 Kg). She had history of hospitalization with the diagnosis of neonatal jaundice with sepsis for 14 days in her neonatal period and that time she was incidentally diagnosed as ASD with mild valvular pulmonary stenosis. Her work-up revealed persistent thrombocytopenia and was evaluated for TORCH infection, CMV IgG was positive, but urine PCR was negative. Since then she had recurrent history of cough that needs consultation almost every fortnight and took treatment with several courses of antibiotics, bronchodilators & cough syrups along with frusemide under supervision of a pediatric cardiologist.

At the age of 9 months, she was admitted twice initially as Bronchiolitis, then Bronchopneumonia with ASD with Heart Failure and finally shifted to cardiac ICU. In Cardiac ICU, she was febrile, cyanotic, severely dyspneic, tachypneic, HR-150, SpO_2:50-60% with repeated attacks of bronchospasm, type 1 respiratory failure and was put on mechanical ventilation, but the very next day she developed subcutaneous emphysema & pneumomediastinum.

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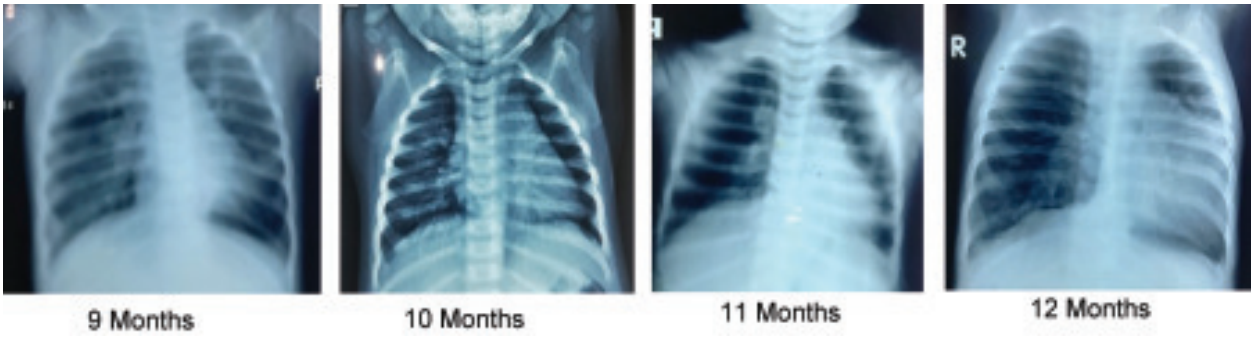

Fig.-1: *Serial chest X-ray*

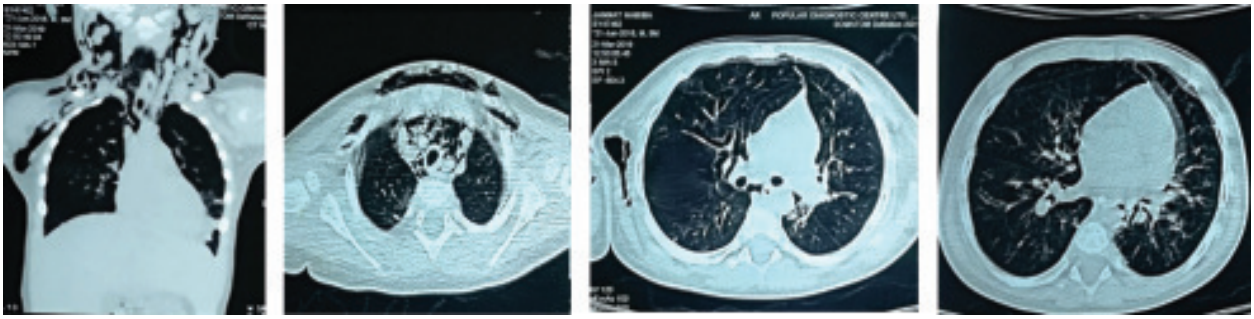

Fig.-2: *CT scan of chest: Pneumomediastinum*

Table-I

Serial CBC showed persistent lymphopenia

	06.03.2019	08.03.2019	01.04.2019	16.05.2019
Lymphocyte count/mm^3	1150\	860	920	730

Blood culture revealed growth of Candida & Acinetobacter and was treated accordingly. Nasopharyngeal swab PCR for RSV & influenza were negative. During the period of mechanical ventilation, she developed hypertension & recurrent attacks of respiratory distress very similar to the attack of severe acute asthma that needs treatment of acute exacerbation. She was evaluated for hypertension and but the reports were all unremarkable. As part of her persistent lymphopenia she was also evaluated for immunodeficiency (also for TB & HIV-report showing normal) and reports showed serum IgA level in lower limit but flow cytometry was suggestive of severe combined immunodeficiency.

Table-II

Flow cytometry at the age of 8 months

Markers	Result(%)	Ref. Value	Result(cells/µL)	Ref value (3-12m)
Gated cells($CD45^+$)				
Lymphocytes	22.5	Up to 61%	1970	3320-7006
T cell markers				
$CD3^+$	91.5	51.8-74.2	1804	2284-4776
$CD3^+$ $CD4^+$	51.7	34.9-53.1	1019	1523-3472
$CD3^+$ $CD8^+$	37.3	12.8-27.1	735	524-1583
$CD4^+$/ $CD8^+$ ratio			1.39	1.48-3.77
B cell markers				
$CD19^+$	6.5	17-37.2	128	776-2238
NK cell markers				
$CD56^+$	1.0	4-15	20	230-801

She needed mechanical ventilation for 10 days. After extubation, she was dyspneic, hypertensive and had repeated attack of bronchospasm every 2-3 day (mostly at night) and stayed in the hospital for about total 4 months. Gradually she became normotensive with medications but was still dyspneic, oxygen dependent and her SpO_2 ranges from 70-80% without oxygen. Finally, she was sent home with O_2 concentrator & cylinder. She was O_2 dependent for another 2-3 months & finally was able to maintain saturation around 88-90% without O_2. Currently, she is maintaining SpO_2 without O_2 since last 3 months but had persistent cough and on & off respiratory distress. Cough is dry, more marked at night with associated night awakening with occasional vomiting. She was alert, playful but tachypneic, normotensive, moderately wasted & stunted but gaining weight very slowly. Chest shape was normal, R/R-42/min, no anemia, no clubbing, breathe sound- vesicular with prolonged expiration with bilateral rhonchi and crepitation. Her recent complete blood count findings were normal, flow cytometry is absolutely normal.

Table-III

Flow cytometry at the age of 18 months

	Result (%)	Ref. Value	Result(cells/µL)	Ref value (3-12m)
Gated cells ($CD45^+$)				
Lymphocytes	44	Up to 61%	6160	3320-7006
T cell markers				
$CD3^+$	61	51.8-74.2	3142	2284-4776
$CD3^+$ $CD4^+$	26	34.9-53.1	1640	1523-3472
$CD3^+$ $CD8^+$	23	12.8-27.1	1416	524-1583
$CD4^+$/ $CD8^+$ ratio			1.09	1.48-3.77
B cell markers				
$CD19^+$	30.3	17-37.2	2450	776-2238
NK cell markers				
$CD56^+$	6.0	4-15	300	230-801

Serum immunoglobulins are also within normal limit. Her color doppler echocardiography, sweat chloride, anti-nuclear antibody (ANA), anti-ds DNA reports are all normal. No reflux was found on contrast X-ray of upper GIT in T-position. But her serial follow up chest x-ray showed persistent infiltrate resembling bilateral ground glass opacity (GGO) and recent high resolution computed tomography (HRCT) showed bilateral GGO, patchy infiltrate, peribronchial thickening as well as mosaic attenuation suggestive of bronchiolitis obliterans.

We could not exclude adenovirus infection in this case due to unavailability of facilities for adenovirus isolation in our country. The facility for lung biopsy in such a small child is also limited and difficult in our country. She is currently on oral prednisolone 1mg/ Kg/day, Hydroxychloroquine 5mg/kg/day, Azithromycin 5 mg/kg/day, Formoterol plus Budesonide meter dose inhaler (MDI) along with nebulized salbutamol SOS.

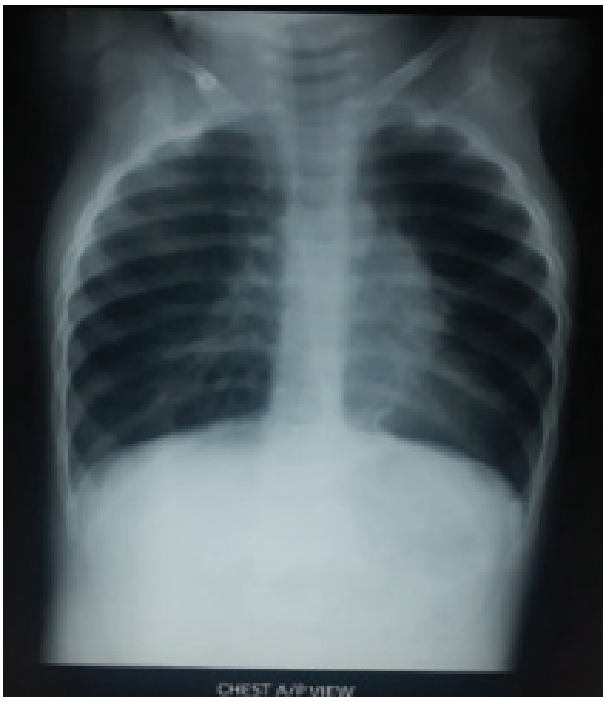

Fig.-4: *Chest X-ray at 17 months*

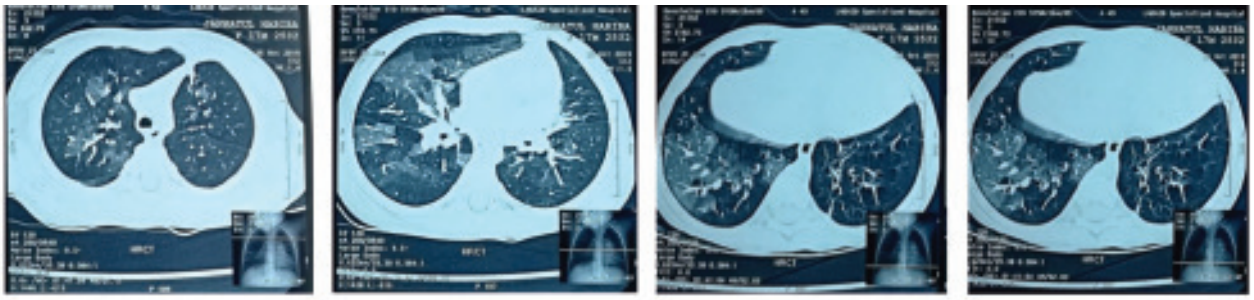

Fig.-5: *High Resolution CT at the age of 17 months*

Discussion

Bronchiolitis obliterans (BO) was first reported and named in 1901 as small airway injury-related chronic inflammation airflow obstruction syndrome that results from bronchiolar epithelial cell and sub-epithelial structural damage due to inflammation.[1,4] BO is divided pathologically into two major categories. The first is proliferative BO (also called pure-type BO), characterized by obstruction of the airway lumen by polyps of granulation tissue. When this granulation tissue extends into the alveoli, the lesion is called bronchiolitis obliterans with organizing pneumonia (BOOP). The second category is constrictive BO, which is characterized by peribronchiolar fibrosis with different degrees of lumen narrowing. Post infectious BO is characterized histologically mainly by a constrictive pattern, with variable degrees of inflammation and airway obliteration where the lung biopsy findings are limited by multifocal pattern of disease. Known etiologies include infections, toxic fume inhalation, connective tissue disease, recurrent aspiration, some drugs, lung and bone marrow transplantation. In many cases, the etiology remains unknown.[6,7]

In our patient, we were not successful to unfold the exact etiology due to our resource limitation in diagnostic facilities. Still our patient had several risk factors like prolonged mechanical ventilation with pneumomediastinum as a complication, prolonged oxygen therapy, severity of infection needed mechanical ventilation, recurrent chest infection and transient immunodeficiency that accentuate the severity. Though BO has been seen to be associated in patients receiving mechanical ventilation for pulmonary conditions, it is still difficult to attribute an etiological role to mechanical ventilation. Some feel it may merely reflect the severity of the underlying insult to the lungs.[2,9] Our patient was ventilated for bronchiolitis associated pneumonia for 10 days and later developed BO. It is possible that the initial injury to the lungs was exacerbated due to mechanical ventilation & its complication. Murtagh et al, evaluated risk factors for BO and death and shown that mechanical assistance was associated to BO in univariate analysis, but in the multivariate model mechanical assistance was no longer related to BO.[3] More than 30 days hospitalization, multifocal pneumonia as initial clinical presentation and hypercapnia were risk factors related to BO in post adenovirus infections.[3] Very few studies have been done in context of BO in children. Colon et al. noted that adenovirus infection and mechanical ventilation were significant risk factors- 34% of patients with post infectious BO required mechanical ventilation compared with only 3% of controls.[4] In a case series of 19 children with post infectious BO, Handy et al. observed that 12 patients were ventilated in the course of initial illness.[5]

Infectious agents of different types have proven role in the development of BO, but the causative role of mechanical ventilation has not been proved, although its association with BO has been noted.[8] While the fact that these children who later develop BO have history of mechanical ventilation, it may just reflect the severity of initial insult. The majority of evidence suggests that BO is immune mediated, so therapeutic interventions have focused on the suppression of inflammatory response.[8] Anti-inflammatory therapy such as corticosteroids, hydroxychloroquine and azithromycin as immunomodulator have been used currently with variable results.[10] Though our case report does not confirm the infectious etiology nor the role of mechanical ventilation in causing BO, further research into the risk factors for BO including the role of mechanical ventilation is warranted. This case is being presented for its rarity and to suggest possibility of prolonged mechanical ventilation as a causative factor in the pathogenesis of BO.

Conclusion

Bronchiolitis obliterans is not very uncommon. The clinical history and HRCT images were essential for the diagnosis and replaces the necessity of invasive procedure. Systemic corticosteroids, hydroxy-chloroquine in combination with azithromycin may offer some benefit for post infectious BO patients.

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