Original Article

Clinical profile and course of children with postinfectious bronchiolitis obliterans from a tertiary care hospital

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ABSTRACT

Background: Postinfectious bronchiolitis obliterans (PIBO) is a chronic obstructive lung disease with scanty information in literature on etiology, clinical profile, treatment, and outcome. **Objective:** The objective of the study is to describe the clinical profile and course of children diagnosed with PIBO. **Methods:** A chart review of children below 18 years of age diagnosed as PIBO over the past 9 years was carried out. Details of clinical profile, laboratory investigations, imaging, treatment received, and outcome were recorded. **Results:** Eight children (boys 4) with PIBO were identified. Median (interquartile range [IQR]) age at the first episode of acute severe bronchiolitis such as illness and diagnosis of PIBO was 15 (6, 23.5) and 30 (16.5, 60) months, respectively, indicating a delay in diagnosis. The most common symptoms were recurrent episodes of cough (100%), fast breathing (100%), wheezing (87.5%), and fever (62.5%). Median (IQR) number of hospitalizations and episodes of antibiotic use prior to diagnosis were 2.5 (2, 5.5) and 2 (2, 4), respectively. Three (37.5%) children received mechanical ventilation during previous hospitalizations. Chest computed tomography revealed mosaic attenuation in 8 (100%), ground-glass opacities in 2 (25%), and bronchial wall thickening in 2 (25%). After diagnosis, 7 received oral steroids, 7 received hydroxychloroquine, 5 received azithromycin, and 2 received azathioprine. The median (IQR) duration of follow-up ($n = 6$) was 6 (1.5, 9.5) months. Median (IQR) number of pulmonary exacerbations in follow-up was 2 (1, 5). **Conclusion:** PIBO is still an under-recognized entity with substantial delay in diagnosis and unnecessary use of antibiotics. Clinical course with imaging findings may help to diagnose and manage this entity.

KEY WORDS: Children, postinfectious bronchiolitis obliterans, mosaic attenuation, steroids

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INTRODUCTION

For the first time in 1901, bronchiolitis obliterans (BO) was described as small airway injury leading to chronic inflammation and airflow obstruction.[1] Various factors, responsible for BO was observed, which include viral infection, inhalation of toxins, and organ transplantation. BO causes inflammation and structural damage to epithelial and subepithelial area of bronchioles.[1] In pediatric population, postinfectious BO (PIBO) is most commonly reported.[2] Adenovirus is the most common viral infection associated with PIBO. One study found that 47.4% of children hospitalized with adenovirus pneumonia developed BO during 5 years of follow-up.[3] Apart from unclear pathogenesis of BO, there is no definitive management, and it carries a poor prognosis.[4] PIBO is often misdiagnosed as recurrent pneumonia, asthma, recurrent aspirations, and other diseases. Clinical data

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are scarce, and many clinicians have limited awareness about BO. Therefore, we conducted this chart review to report experience on PIBO at our center. Our objective was to describe the clinical profile and course of children diagnosed with PIBO.

METHODS

We retrospectively reviewed records of children <18 years of age diagnosed with PIBO between January 2010 and December 2018 in the Pediatric Pulmonology Division, Department of Pediatrics of a Tertiary Care Hospital in India. PIBO was diagnosed in children who had not recovered completely from acute bronchiolitis like illness even after 6 weeks and had waxing and waning episodes of wheezing later on along with the evidence of small airway disease in high-resolution computerized tomography of chest as suggested by mosaic perfusion with air trapping. Children with diffuse lung diseases such as cystic fibrosis, primary ciliary dyskinesia, aspiration syndromes, and interstitial lung disease were excluded by appropriate investigations if clinically indicated. The open lung biopsy was considered in selected patients where the diagnosis of PIBO was uncertain. Data on demographic profile, clinical features, laboratory investigations, imaging, and management were collected. The treatment protocol of unit for PIBO included: systemic steroids 1–2 mg/kg/day to achieve symptomatic improvement and gradual tapering, inhaled steroids 200–400 μg/day in two divided doses by metered-dose inhaler and spacer with face mask, and hydroxychloroquine. Other drugs such as azithromycin were started in refractory symptoms. Steroid sparing agent such as azathioprine (2–3 mg/kg/day) was added if the patient deteriorated on tapering of systemic steroids. Children presenting with acute exacerbations were assessed for super-added infection by clinical features, comparing fresh X-ray film of chest with previous chest X-ray (CXR) and other indicators of infection like C reactive protein/procalcitonin/total and differential counts of blood. Infection was treated with broad-spectrum antibiotics. After ruling out infections, systemic steroids were increased, or pulse methyl prednisolone was given to control symptoms. To identify risk factors for severe PIBO, children were divided into two groups based on more than or less than one hospitalization per 6 months' period from onset of symptoms to the last follow-up visit. These two groups were compared for age, age of symptom onset, gender, anthropometry, mechanical ventilation, oxygen dependency, and treatment. The study was approved by institute's ethics committee.

Statistical analysis

Data were managed using Microsoft excel and analyzed using STATA version 13 (StataCorp. College Station, TX, USA). Descriptive statistics were used to present the data.

RESULTS

A total of 8 children fulfilled diagnosis of PIBO (boys 4; median [interquartile range (IQR)] age 30 [16.5, 60] months). The median (IQR) age at first episode of acute severe bronchiolitis such as illness and diagnosis of BO was 15 (6, 23.5) and 30 (16.5, 60) months, respectively. Median (IQR) z-score for weight (kg) and height (cm) was −1.35 (−2.11, −0.42) and −0.05 (−1.4, 0), respectively. One child was born preterm and two received respiratory support at birth. None had a family history of asthma or allergy. The most common symptoms were recurrent episodes of cough (100%), fast breathing (100%), wheezing (87.5%), and fever (62.5%) following first acute episode. Median (IQR) number of hospitalizations and episodes of antibiotic use prior to diagnosis was 2.5 (2, 5.5) and 2 (2, 4), respectively. All children (100%) received oxygen and 3 (37.5%) children received mechanical ventilation during previous hospitalizations. Two (25%) children received at least one course of antitubercular therapy (ATT) prior to diagnosis. Partial response to bronchodilators was seen in 5 (85.7%). Most of the children were not diagnosed with BO before coming to our institute. Table 1 summarizes the demographic profile, clinical features, and imaging findings. CXR and computed tomography (CT) images of case 4 and case 6 are shown in Figures 1 and 2, respectively.

Seven (87.5%) children had clubbing and 7 (87.5%) had rhonchi on examination at presentation. Bronchoscopy was done in five, and it was abnormal in two; one had

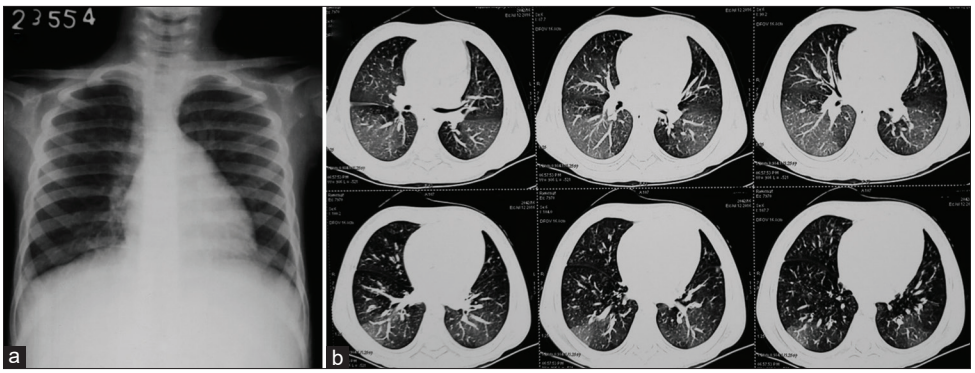

Figure 1: Chest X-ray and computed tomography chest of case 4: (a) Chest x-ray showing hyperinflation, (b) computed tomography chest is showing mosaic attenuation and centrilobular nodules

Table 1: Demographic profile, clinical features, and imaging of children with bronchiolitis obliterans

	Patient number							
	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**
Age at first episode (months)	23	6	6	24	12	18	2.5	30
Age at diagnosis of BO (months)	24	13	62	60	20	60	6	36
Current age (age at last follow-up visit) (months)	31	16	62	88	20	68	16	41
Duration of follow-up (months)	7	3	0	28	0	9	10	5
Gender Male/female	Male	Male	Male	Female	Female	Male	Female	Female
Number of exacerbations in follow-up	5	2		8		2	2	3
Weight (*Z*-score)	−0.25	−3.5	−0.31	−1.8	−1.28	−0.26	−1.82	−1.36
Height (*Z*-score)	−0.95	−4.87	−2.19			−1.07		0.57
Clubbing (yes/no)	Yes	No	Yes	Yes	Yes	No	No	No
CXR findings	Collapse	Hyperinflation		Hyperinflation [Figure 1a]	Collapse	Hyperinflation [Figure 2a]	Bilateral diffuse haze	
CT findings	Mosaic attenuation, GGOs	Mosaic attenuation. Central bronchiectasis, bronchial wall thickening	Mosaic attenuation with hyperinflation	Mosaic attenuation with centrilobular nodules [Figure 1b]	Mosaic attenuation with air trapping	Mosaic attenuation, peribronchial thickening [Figure 2b]	Mosaic atttenuation, collapse postr segment RUL, fibroatelectasis LUL	GGOs with mosaic attenuation
Treatment received	Steroids, pulse steroids, azithromycin, HCQ, azathioprine	Steroids, azithromycin, HCQ, tiotropium	Steroids, azithromycin, HCQ. lasilactone	Steroids, HCQ, azathioprine	Inhaled steroids	Steroids, azithromycin, HCQ, tiotropium	Steroids, HCQ, ICS azithromycin	Sterods, HCQ, ICS
Current status	Home oxygen	Stable	Lost to follow-up	Stable	Lost to follow-up	Stable	Stable	Stable

BO: Bronchiolitis obliterans, HCQ: Hydroxychloroquine, ICS: Inhaled corticosteroid, GGOs: Ground-glass opacities, RUL: Right upper lobe, LUL: Left upper lobe, CXR: Chest X-ray, CT: Computed tomography

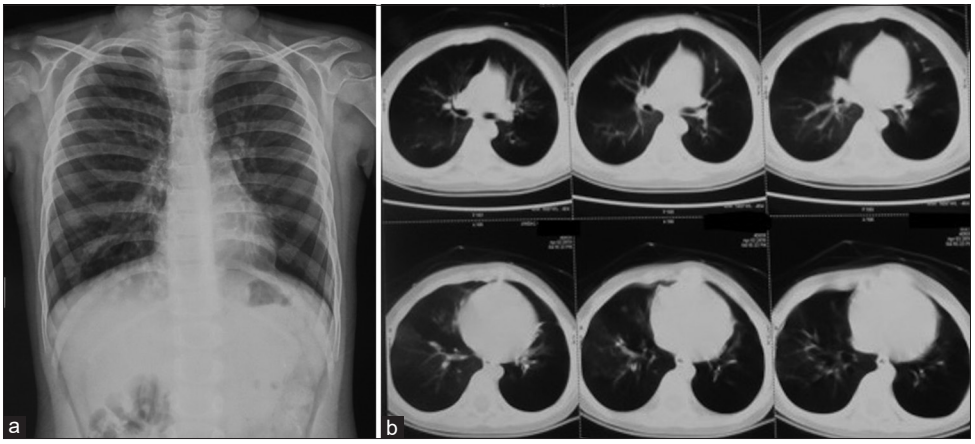

Figure 2: Chest X-ray and computed tomography chest of case 6: (a) Chest X-ray showing hyperinflation, (b) computed tomography chest is showing mosaic attenuation and peribronchial thickening

lower tracheomalacia with dynamic obstruction of the right bronchus, and one had laryngomalacia. Barium swallow and esophageal nuclear scan were performed in four and was reported as normal in all. CXR reports were available in six patients out of whom two had hyperinflation, two had collapses, and two had both hyperinflation along with collapse.

Chest CT revealed mosaic attenuation in 8 (100%), ground-glass opacities in 2 (25%), and bronchial wall thickening in 2 (25%). Open lung biopsy was performed in 1 child (case 6) and it was suggestive of BO. All eight children received supportive care including oxygen inhalation, inhaled corticosteroids, and bronchodilators. Further, 7 (87.5%) each received additional oral steroids and hydroxychloroquine, and 5 (62.5%) received azithromycin. Three children (37.5%) were discharged on home oxygen and one child was still oxygen dependent during the last follow-up. Two (25%) children were lost to follow-up after diagnosis. The median (IQR)

duration of follow-up was 6 (1.5, 9.5) months, and the number of pulmonary exacerbations was 2 (1, 5). The median number of hospitalization before diagnosis and in follow-up after diagnosis was 2.5 (2, 5.5) and 1 (0.5, 1.5), respectively, and it suggested markedly decreased in number of hospitalization after starting treatment for BO (P = 0.06). The median number of hospitalizations from the age of onset of symptom till the last follow-up was 4 (2, 8). There was no difference in age of symptom onset, age of diagnosis, gender, anthropometry, oxygen dependency, and mechanical ventilation in children who had less than one episode of hospitalization per 6 months (from onset of symptoms to the last follow-up visit) compared those who had more than one episode of hospitalization per 6 months [Table 2].

DISCUSSION

There are a very few case series on PIBO. Li *et al*. from China reported 42 cases of PIBO where adenovirus (in 50%) followed by mycoplasma (in 23.8%) were the most common causes of PIBO.[5] Colom *et al*. from Baltimore in a case–control study of 109 cases and 99 controls identified bronchiolitis due to adenovirus and need for mechanical ventilation as strong risk factors for BO.[6] In a study from Chile, Castro-Rodriguez *et al*. followed 45 cases of adenovirus pneumonia for 5 years and reported BO in 18 cases in follow-up and these were severe cases of adenovirus pneumonia.[3]

Ours is one of the first series on PIBO in children from developing countries. BO was traditionally considered to be a rare clinical entity in children. In our series, majority of patients had lower respiratory tract infections during the initial 2 years of life who received hospitalization and oxygen support prior to establishment of the diagnosis. In previous reports, the prevalence of BO was observed to be higher in boys than girls.[7,8] However, in our series, girls were equal to boys. One-fourth of children received ATT prior to establishment of diagnosis which highlights the fact of unawareness of BO and the empirical use of ATT in recurrent pulmonary symptoms among clinicians in set-up like us. Fibrosis of small bronchioles results in no or inadequate response to inhaled bronchodilators, which is shown in our patients that most of them had only partial response to inhaled bronchodilators. The presence of clubbing in 87.5 children suggests the degree of hypoxemia they suffered due to BO prior to presentation to our center which indirectly suggests the delay in diagnosis. As ours is a small case series, statistically significant difference in age of symptom onset, age of diagnosis, gender, anthropometry, oxygen dependency, and mechanical ventilation in children with frequent hospitalizations compared to those of infrequent hospitalization could not be seen. The clinical history of waxing and waning obstructive respiratory symptoms and CT chest images were important for the diagnosis of BO in our study apart from excluding other diffuse lung diseases by appropriate investigations. Open lung biopsy although said to be the gold standard, is usually not required for the diagnosis of BO. This invasive investigation may be considered in patients whom diagnosis is doubtful and show progressive deterioration even after treatment. In our patients, one (12.5%) underwent open lung biopsy when the diagnosis of BO was in doubt.

The definitive treatment for PIBO is not yet established. The current treatment modalities include supportive care, steroids, azithromycin, and mechanical ventilation depending on the severity of respiratory distress.[8,9] Systemic corticosteroids and oral azithromycin were shown to be effective in PIBO from few studies.[2,10] Long-term use of azithromycin was found to improve forced expiratory volume in 1 s in postlung-transplant BO along with reduced airway neutrophilia and interleukin-8 levels.[11,12] Mechanical ventilation is imperative for the support of children with respiratory insufficiency. In our patients, 3 (37.5%) children received mechanical ventilation prior to diagnosis as supportive measures due to respiratory failure. We found some improvement with oral steroids and other adjuvant therapies in our study.

Strengths of our study are that this is one of the few series of PIBO in children from developing country and there was marked improvement in hospitalization after starting therapy for BO. Limitations of our study were retrospective design with a small number of patients, lack of identification of viral etiologies, and relatively short follow-up.

CONCLUSION

PIBO is still an under-recognized entity with substantial delay in diagnosis and unnecessary use of antibiotics and ATT. Clinical features with imaging findings may help to diagnose and manage this entity. Systemic steroids, in

Table 2: Comparison of children with bronchiolitis obliterans having hospitalization less than and more than one per 6 months' duration

Characteristic	Less than one hospitalization per 6 months (*n*=4)	More than one hospitalization per 6 months (*n*=4)	*P*
Age of symptom onset (months)	12 (4.25-21)	17.5 (9-26.5)	0.467
Age of diagnosis (months)	60 (33-61)	22 (16.5-30)	0.245
Urban/rural	3/1	4/0	0.285
Male/female	2/2	2/2	1.000
Weight (*Z*-score) at diagnosis	−1.27 (−2.11-−0.42)	−1.35 (−2.55- −0.72)	1.000
Mechanical ventilation, *n* (%)	2 (50)	1 (33.3)	0.465
Home oxygen, *n* (%)	0 (00)	1 (33.3)	0.285

combination with other immunomodulatory drugs, may offer some benefit for children with BO.

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Conflicts of interest
There are no conflicts of interest.

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