Original Article

The clinico-radiological profile of obliterative bronchiolitis in a tertiary care center

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ABSTRACT

Background: Obliterative bronchiolitis (OB) forms a major proportion of chronic airway diseases (CADs). OB is often misdiagnosed and included under the umbrella term 'chronic obstructive pulmonary disease'. We set out to identify the proportion of OB cases among the CADs and study the clinical profile of OB. **Materials and Methods:** This prospective, observational study noted all patients with Chronic airway obstruction (CAO), of which patients with OB were included and the clinical profile was studied. Data were subjected to statistical analysis. **Results:** Five hundred patients with CAO were noted in the study period, of which 115 patients were found to be OB amounting to a prevalence of 23%. The mean age of presentation was 51.8 years (standard deviation 12.1) with a male–female ratio of 1:1. The most common etiology for OB was as sequelae to past treated pulmonary tuberculosis (PTB) seen in 82 patients (71%) of cases. Dyspnea in 114 patients (99%) and productive cough in 110 patients (95%) were the predominant symptoms. Postexercise desaturation was seen in all 115 patients (100%). Forty-six patients (43%) presented with either Type 1 or Type 2 respiratory failure. Spirometry showed obstructive pattern in 68 patients (59%) with forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio of <70% and FEV1 <70% postbronchodilator and mixed pattern in 47 patients (41%) with a reduction in both FEV1 and FVC and normal FEV1/FVC ratio. There was the presence of mosaic attenuation on high-resolution computerized tomography (HRCT) of the chest with expiratory scans in all 115 patients (100%). Pulmonary hypertension was documented in 109 patients (95%). **Conclusion:** OB is one of the major causes of CAO. HRCT of the chest with expiratory scans plays a important role in the diagnosis. Early diagnosis can prevent irrevocable complications.

KEY WORDS: Chronic airway diseases, mosaic attenuation, obliterative bronchiolitis

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INTRODUCTION

Chronic airway disease (CAD) contributes to very significant magnitude of respiratory mortality and morbidity. It includes bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), bronchiectasis, and obliterative bronchiolitis (OB). OB is characterized by extensive involvement of small airways. Clinical manifestations are not apparent until 80% of airways are involved leading to delayed diagnosis and delayed treatment. OB leads to airway remodeling and culminates in irreversible fibrosis of bronchiolar wall. Customary etiologies comprise viral pneumonia,[1] toxic fumes exposure,[2] postrespiratory infection,[1,3] connective tissue disorder,[4] drug exposure,[5] organ transplantation,[6] thyroiditis,[7-9] *Sauropus androgynus*,[10] and due to human immunodeficiency virus (HIV) infection. These cases

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are frequently misdiagnosed with COPD or BA[11] due to the overlap in symptomatology and clinical findings. The diagnosis is aided by the Turton's clinical criteria[12] which are an amalgamation of clinical features, radiology, and spirometry findings. High-resolution computerized tomography (HRCT) of the thorax plays an important role in establishing the diagnosis. The classical picture is sharply defined areas of decreased lung attenuation associated with vessels of pulmonary vasculature of decreased caliber. These changes represent a combination of air trapping and oligemia.[13,14] This combination can give a mosaic attenuation pattern, which worsens on expiratory scan.[15] This worsening of the patchy white and dark areas on expiratory scans also termed as mosaic perfusion is the hallmark feature which typifies OB.[13-15] Treatment depends on the root cause responsible for causing OB and the associated disorder. Since there are no separate guidelines pertaining to postinfectious OB, it is treated as per treatment guidelines for COPD. OB due to other causes has different treatment protocols. Macrolide antibiotics have a role as immunomodulators. Low-to-medium-dose inhaled corticosteroids with or without bronchodilators also aid in relieving the airway inflammation and obstruction. Sequelae of OB include recurrent episodes of Type 2 respiratory failure, pulmonary hypertension (PH), cor pulmonale, and right heart failure (RHF). These lead to multiple hospitalizations and significant morbidity, mortality, and also contribute to burden on healthcare services. This is to a great extent preventable by the early diagnosis and proper management.[16,17] The present study was carried out to study the clinico-radiological profile of OB in a tertiary care center.

MATERIALS AND METHODS

A prospective observational study for a year was conducted in the Department of Pulmonary Medicine of a tertiary care hospital in Mumbai after the Institutional Ethics Committee approval. In this study, 500 consecutive patients who presented with a history of chronic airway obstruction (CAO) were screened, of which 115 patients diagnosed with OB as per the Turton's criteria were enrolled in the study. The Turton's criteria[12] are as follows: (a) irreversible airway obstruction, (b) reduced forced expiratory volume in 1 s (FEV1), and (c) exclusion of COPD, asthma, bronchiectasis, or any other known causes of airway obstruction with the utility of history and relevant investigations. Demographic data in the form of age and sex were obtained. A detailed history of symptoms in the form of cough, sputum production, dyspnea, and chest pain was taken. Furthermore, the history pertaining to the causes of OB such as the history of prior infection, exposure to toxic fumes or toxic gas inhalation, connective tissue disorder, intake of certain drugs, and lung transplant was taken. Comorbidities and addictions were noted. A detailed general and systemic examination was done. Pulse oximetry was performed for documenting baseline saturation as well as postexercise desaturation. Special investigations for diagnosis of OB was done, in the form of arterial blood gas analysis (ABG), chest radiograph (CXR), spirometry to measure the FEV1, forced vital capacity (FVC) and FEV1/ FVC ratio, two-dimensional echocardiography (2D echo), and HRCT of the thorax with expiratory scans in all patients. Initially, the proportion of OB cases among CAO was calculated to assess the prevalence of OB. Then, the profile of OB was studied in the form of demography, clinical picture, radiological findings, spirometry findings, and relevant supportive investigations. Data were analyzed and presented in percentages and mean.

RESULTS

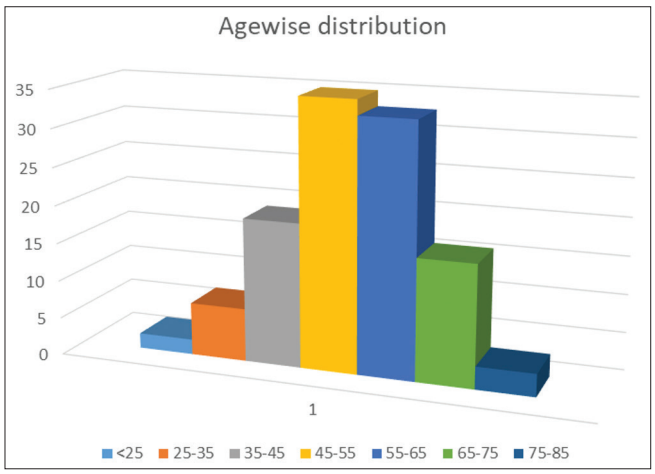
Of the 500 patients who presented with the history of CAO, 115 cases were found to be OB. The prevalence of OB thus was 23%. Of these, 58 (50%) were male patients, whereas 57 were female (50%) [Table 1]. Mean age of the study group was 51.8 years, (SD 12.1 years) (SD 12.14; Range 21-78 yrs). Most of the patients fell in the age group of 35–65 years comprising 87 patients (75%) [Graph 1]. The average duration of the disease was 6.9 years ([SD]-6.1). The most common presenting symptom was cough in 110 (95%) patients and dyspnea in 114 (99%) patients. The most common cause of OB was as a sequelae to old treated PTB in 82 patients (71%) followed by childhood pneumonia accounting for 20 (17%) of the cases. Other rare etiologies encountered were rheumatoid arthritis (RA) associated 2 (2%), HIV associated 1 (1%), thyroiditis-associated OB 3 (3%), and cotton dust exposure-associated OB 1 (1%). Idiopathic OB was seen in 5% of cases [Graph 2]. Most commonly seen comorbidity was systemic hypertension in 24 patients (20%), diabetes mellitus in 17 patients (14%), connective tissue disorder in four patients (3%), thyroid disorder in five patients (4%), and IHD in six patients (5%). On general examination, the salient findings were clubbing was in 26 patients (22%) followed by pedal edema in 15 patients (13%). Postexercise desaturation was observed in all patients (100%). On respiratory system examination, crackles were heard in 107 patients (93%), whereas rhonchi were appreciated in 56 patients (48%). ABG analysis showed Type 1 respiratory failure (hypoxia) in 26 patients (22%) and Type 2 respiratory failure (hypoxia with hypercapnia) in 20 patients (17%) at presentation, whereas the remaining patients had a normal ABG report.

Radiologically, the most common abnormality seen on CXR was the presence of fibrosis in 48 patients (42%), followed by lobar collapse in 28 patients (25%). CXR was normal in 18 (16%) patients. Other sporadic findings were the presence of cardiomegaly, pleural effusion,

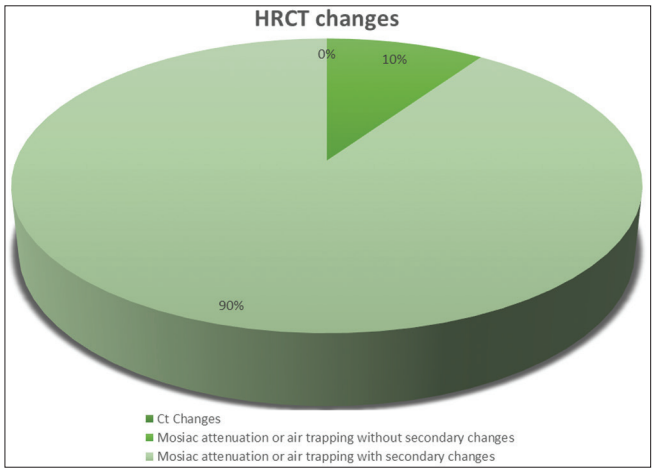
Table 1: Showing the demographic distribution

Sex	Number of patients	Percentage
Male	58	50
Female	57	50
Total	115	100

and hyperinflation. On HRCT of the chest, mosaic perfusion without the presence of secondary changes was seen in 11 patients (10%), and mosaic perfusion with the presence of secondary changes was seen in 104 patients (90%) [Graph 3 and Figures 1, 2]. Spirometry showed the presence of obstructive abnormality in 68 patients (59%) with poor postbronchodilator reversibility and mixed abnormality in 47 patients (41%). Forty-one patients (38%) presented with moderate obstruction with FEV1 between 50% and 80% predicted, 40 patients (35%) presented with severe obstruction with FEV1 between 30% and 50% predicted, and 31 patients (27%) presented with very severe obstruction with FEV1 being <30% predicted [Table 2]. 2D echo demonstrated mild PH in 77 patients (67%), i.e., pulmonary artery systolic pressure (PASP) estimated indirectly by the tricuspid regurgitation jet method, between 30 and 45 mmHg, six patients had no PH (5%), whereas 20 patients (17%) had moderate PH, with PASP between 45 and 60 mmHg, and 12 patients (11%) had severe PH, with PASP >60 mmHg.



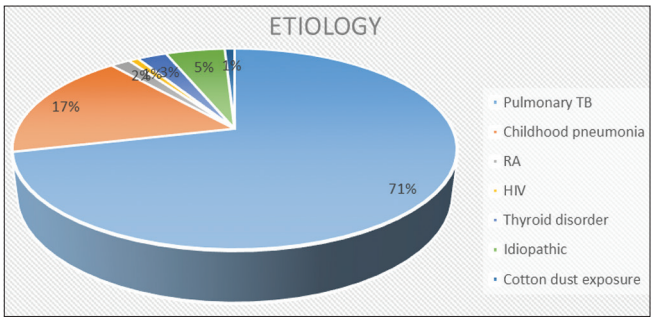
Graph 1: Bar diagram showing the age distribution of obliterative bronchiolitis



Graph 3: Pie diagram showing the CT changes in Obliterative bronchiolitis

DISCUSSION

OB or constrictive bronchiolitis is a specific cause for CAO and is caused due to obliteration of the respiratory bronchioles or the small airways due to any infectious or immunological insult. The prevalence of OB in this study was 23% in the study population recruited. This was in concordance with other Indian studies where the prevalence of OB was found to be between 16% and 25%.[11,16] The awareness among clinicians about the existence of OB is dismal and OB is usually lumped under the umbrella term COPD owing to its clinical and radiological resemblances. However, distinguishing between the two plays an important role in the early identification of the disease, for specific therapy and prognostication.[17] Hence, this study aimed at estimating the prevalence of this entity and also to assess its profile in clinical practice. Mean age of the presentation of OB in this study was 51.8 years (SD 12.14 years). Majority of patients fell in the age group of 35–65 years. This was in concordance with most of the Indian studies which suggest that usual presentation of OB is seen after the age of 40 years.[11,16] OB is characterized by extensive involvement of small airways. Clinical manifestations are not apparent until approximately 80% of airways are involved. The anatomy and wide surface area of small airways are the basic mechanism behind this phenomenon. Hence, usually manifestations of OB become clinically detectable after an ample period of primary insult. Incidence of OB in this study was same in both males and females amounting to 50% each. As such there is no sexual predilection for the occurrence of OB. There is a significant overlap between symptomatology of OB and other CADs such as BA and COPD. The predominant symptoms are



Graph 2: Pie diagram depicting the various etiologies for obliterative bronchiolitis

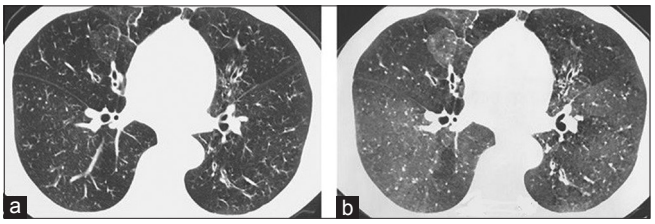


Figure 1: High Resolution Computarised Tomography showing the presence of mosaic attenuation in (a) and worsening on expiratory scan in (b)

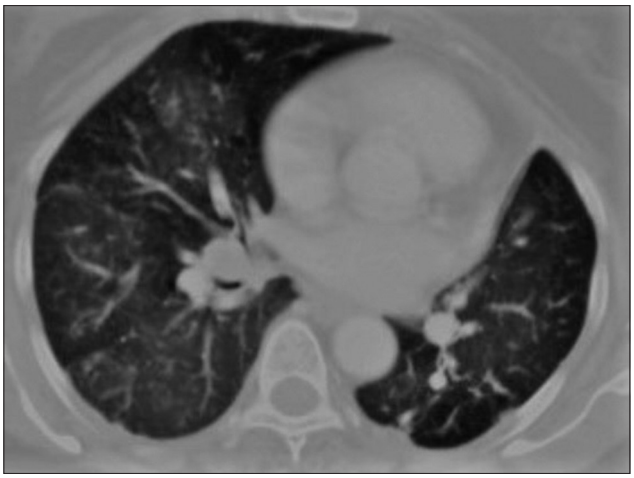


Figure 2: High-resolution computerized tomography showing the presence of mosaic attenuation with fibrosis

Table 2: The grades of obstruction on Spiromtery

Grading of obstruction	Number	Percentages
Mild (FEV1 >80%)	0	0
Moderate (FEV1 50-80%)	44	38
Severe (FEV1 30-50%)	40	35
Very severe (FEV1 <30%)	31	27

productive cough and progressive exertional dyspnea which were encountered in this study too.

In this study, the predominant etiology was postinfectious as seen in 88% of cases as against western countries where OB is commonly associated with the lung, heart–lung and bone marrow transplant, and collagen vascular diseases. Postinfectious nature of the disease was based on temporal relationship with the previous history of childhood pneumonia or pulmonary tuberculosis (PTB), and the diagnosis was made long after the initial insult. In 82 patients (71%), symptoms of CAO began following an episode of PTB. The diagnoses in these cases were obtained from the past records available with the patient. OB following lung infections with *Mycobacterium avium* intracellular and *Mycobacterium tuberculosis* have been reported in the literature.[18] In India, since the prevalence of tuberculosis is high, it is likely to be an important cause of OB. In a study in Chicago in 1960, of 1403 patients of TB admitted 23% had chronic airflow limitation.[19] In 82 patients (71%) symptoms of chronic airway obstruction began following an episode of pulmonary tuberculosis.[20] In another study by Joshi *et al*., 12 patients who were misdiagnosed with asthma, COPD, and bronchiectasis were found to have OB which was seen secondary to past tuberculosis or past infections. The result obtained in this study was concordant with this Indian study on OB.[16] Other rare causes of OB were those which were secondary to thyroiditis associated,[7-9] RA associated, HIV associated, and cotton dust exposure-associated OB which was seen in 3 (3%), 2 (2%), 1 (1%), and 1 (1%) of the patients, respectively. The diagnosis of etiology in these cases of OB was by demonstration of the presence of thyroid peroxidase antibodies in a case of thyroiditis-related OB, demonstration of RA factor in RA-associated OB, seropositive status in HIV-associated OB, and the history of exposure in occupation associated OB. When all other causes of OB have been ruled out, and clinically patient presents with progressive dyspnoea and cough with post excercise desaturation,spirometry suggestive of obstructive abnormality ,and HRCT of the thorax suggestive of air trapping without any secondary changes then diagnosis of idiopathic OB is done.[8] It is the diagnosis of exclusion and was seen in 6 (5%) patients in this study.

Most characteristic feature on examination which is pathognomonic of OB is the presence of postexercise desaturation which was seen in all our patients. As OB is known to progress rapidly, many patients may primarily present with cor pulmonale and RHF[17] manifesting in form raised jugular venous pressure and pedal edema which was seen in 15 patients (13%). As the disease is usually seen after a prolonged period of previous insult, and has a rapid progression to RHF, the patient may present primarily in exacerbation with either Type 1 respiratory failure which was observed in 26 patients (20%) or in Type 2 respiratory failure which was detected in 20 patients (17%) patients. CXR in OB[13] may show the presence of sequelae of past infections which may be appreciated in the form of fibrosis which was seen in 48 patients (42%), collapse which was appreciated in 28 patients (25%), and cystic opacities in 14 patients (12%). Sometimes, CXR may be normal as seen in 18 patients (16%). Other findings may be in the form of changes hyperinflation because of the underlying air trapping which may be confused with COPD. Spirometry findings of OB include a reduced FEV1, reduced FVC, and a normal or reduced FEV1/FVC ratio. A paradoxical fall in FEV1/FVC may be seen in patients with OB following effective treatment due to preferential opening of the small airways, resulting in reduction in air trapping, and improvement in FVC.[21] In this study, obstructive pattern was seen in 68 patients (59%) and mixed pattern was seen in 47 patients (41%). Moderate obstruction was observed in 44 patients (38%), severe obstruction was seen in 40 patients (35%), and very severe obstruction was documented in 31 patients (27%). This is in concordance with other studies where the number of patients having severe-to-very severe obstruction is more.[16] This may be due to late detection of the disease and due to significant small airway involvement.

The diagnosis of OB can be confirmed by the characteristic HRCT findings in the correct clinical context.[13] The definitive findings for OB include heterogeneity of lung density, i.e., patchy areas of high and low attenuation of the lung parenchyma ("mosaic pattern/mosaic perfusion") thought to be a consequence of reflex vasoconstriction in under-ventilated areas of the lung. This finding is exaggerated on expiratory HRCT scan due to air trapping. Other features include fibrosis, scarring, and bronchial dilatation when OB is seen as sequelae to past infections.

In a study by Hansell *et al*.,[22] it was found that such changes of mosaic attenuation due to OB are common in bronchiectasis, and suggested that in these cases, OB might have been an early event in the pathogenesis. In most cases, childhood respiratory infections cause either bronchiectasis or OB; however, in some individuals, both bronchiectasis and OB may result.[22] Mosaic attenuation was seen in all patients confirming the diagnosis of OB. Mosaic attenuation with secondary changes, i.e., in form of associated fibrosis, bronchial wall dilatation, peribronchial thickening, collapse, and bronchiectasis was appreciated in 104 patients (90%). Mosaic attenuation without any secondary changes was documented in 11 patients (10%). Usually, the presence of only mosaic attenuation is seen in cases of thyroiditis-associated OB, RA-associated OB, HIV-associated OB, and idiopathic OB. OB has been reported as an important cause for PH and cor pulmonale.[11,18] This occurs due to chronic hypoxia-induced pulmonary vasoconstriction, vasodestruction, or vaso-obliteration by thrombotic events. In this study, mild PH was seen at diagnosis in 77 patients (67%), moderate PH in 20 patients (17%), and severe PH in 12 patients (11%). This is in concordance with other studies of OB where mild PH is seen in majority of patients.[11,16,17]

Treatment of bronchiolitis varies on the underlying cause or the associated disorder. Response to therapy and prognosis, in general depends on the stage of disease and whether the disorder is airway or interstitial. Constrictive bronchiolitis is generally progressive with minimal response to therapy, and corticosteroids have little role in treating bronchiolar disorders associated with this lesion. Most commonly seen OB in developing countries is of postinfectious etiology. There are no specific guidelines for the management of the same, and usually, the GOLD guidelines are followed for treatment. It is managed with inhaled corticosteroids and orally inhaled bronchodilators. In cases of toxic inhalation injury-associated OB, corticosteroids are occasionally effective in the management of both the acute-phase illness (pulmonary edema) and the late-phase illness (bronchiolitis obliterans). Macrolide antibiotics have been reported to improve symptoms and lung function in airway bronchiolar disorders.[23,24] Macrolides impair neutrophil-derived elastolytic activity in the lung and also decrease the total number of neutrophils in BAL.[23,24] They are also effective in reducing the circulating pool of T lymphocytes and attenuating the immune response. The appropriate drug or the dosage has not been studied adequately, and no controlled data exist. Low doses of oral erythromycin (200–600 mg/day), clarithromycin (25–500 mg/day), or azithromycin (250 mg every other day) usually for 6 months have been recommended for most of the patients.[25,26] Etanercept is found to be effective in a clinical trial of patients with connective tissue disease-associated bronchiolitis obliterans.[26] Treatment of cryptogenic organizing pneumonia depends on the underlying cause and treating or removing the causative exposure. The mainstay treatment of organizing pneumonia is corticosteroids. Prednisone is recommended as the first-line treatment for patients with symptomatic and progressive disease.[18] Characteristically, clinical improvement occurs within a few days, followed by the resolution of radiographic opacities within a few weeks. Prednisone therapy is initiated at 0.75–1 mg/kg and tapered by 0.25 mg/kg every 4 weeks, for a total duration of 6 months–1 year.[25,26] Since a 6-month course may be sufficient in certain situations, rapid weaning may be attempted. Relapses may occur in 10%–40% of patients on dose reduction or cessation of therapy.[18]

As the study was done in limited number of patients, the large multicentric study needs to be done for the same for the confirmation of the above findings as also determine the response to therapy.

CONCLUSION

OB is one of the major causes of CAO which is largely underdiagnosed and underreported. This phenomenon is chiefly due to its symptomatic overlap with other more common cause of CAO and lack of awareness regarding its profile. It leads to significant airway obstruction, distressing symptoms, morbid sequelae, poor quality of life, and eventually mortality from respiratory failure. The diagnosis can be expedited by maintaining a high index of suspicion, meticulous history taking, and a timely HRCT of the thorax with expiratory scans and spiromtery to know the degree of obstruction. Based on the underlying etiology, appropriate therapy can be initiated to forestall the development of further complications. Early diagnosis can prevent the ensuing morbidity and mortality and thereby decrease the burden on healthcare services.[11,17]

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Conflicts of interest
There are no conflicts of interest.

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