

Clinico-Radiologic and Spirometric Profile of an Indian Population with Post-Tuberculous Obstructive Airway Disease

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ABSTRACT

Introduction: Tuberculosis is a public health problem in developing countries and in spite of receiving adequate anti-tuberculous therapy, patients often continues to have several post-tuberculous sequelae, especially airflow limitation.

Aim: To evaluate pulmonary function by spirometry among post-tuberculosis cases with airway obstruction and their relationship with smoking.

Materials and Methods: All patients who presented to the pulmonary medicine Outpatient Department (OPD) with symptoms of obstructive airway disease and had completed adequate anti-tuberculous therapy for pulmonary tuberculosis were taken up for study. They were initially evaluated with sputum smear for Acid Fast Bacilli (AFB) and chest X-ray. Patients without evidence of active tuberculosis underwent spirometry and those having post-bronchodilator Forced Expiratory Volume in first second (FEV1)/ Forced Vital Capacity (FVC) FEV1/FVC<0.7 were taken up for

final analysis. Spirometric parameters were compared between smokers and non-smokers.

Results: Out of 138 finally selected cases, 84.06% were male and 71.01% were within age range of 40-69 years. Significant positive association was found between extent of radiologic lesion and severity of airflow obstruction. Purely obstructive pattern was found in 27.54% cases and 72.46% showed mixed pattern. Patients with mixed ventilatory abnormality had worse pulmonary function and poorer bronchodilator reversibility than patients with pure obstruction. Comparison of post-bronchodilator FEV1, FVC, Peak Expiratory Flow (PEF) and Forced Expiratory Flow (FEF) 25-75 between smokers and non-smokers did not show statistically significant difference.

Conclusion: Majority of patients with post-tuberculous obstructive airway disease have associated restrictive component. But smoking did not cause significant alteration in pulmonary function among such patients.

Keywords: Chronic obstructive pulmonary disease, Peak expiratory flow, Forced expiratory flow

INTRODUCTION

Tuberculosis (TB), being a disease known to mankind since many centuries, continues to be a public health menace, especially in the underdeveloped countries. On the other hand, global incidence of Chronic Obstructive Pulmonary Disease (COPD) and other obstructive airway diseases are gradually increasing owing to increased risk factors of airflow limitation. According to the global burden of disease and risk factors, COPD and TB are among the top ten causes of death and disability for underdeveloped countries at the beginning of the 21st century [1].

Several previous studies suggested an association between Pulmonary Tuberculosis (PTB) and airflow limitation, which were conducted in Africa [2-4], and in Asia [5-8]. A South African study, which was done on subjects who had previously been treated for PTB up to sixteen years ago, also showed that 68% of the patients had chronic obstructive lung disease [9]. Thereby, it can be said that patients surviving PTB are left with permanent damages in lung architecture and are at higher risk of pulmonary sequelae. Although TB has also been mentioned as a risk factor of COPD in recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [10], current definition of COPD does not include infectious aetiology. Thereby, we preferred the "Obstructive Airway Disease (OAD)" terminology over COPD in our study.

As we usually presume, smoking is the major risk factor for airway obstruction [10], but the number of studies attempting to prove the effect of this potential confounder on the relationship between prior TB and airflow limitation are very few [11,12]. Although India has a huge burden of both TB and COPD and is one of the biggest consumer of tobacco products in the world, there is lack of

information about potential role of smoking on the development of post-tuberculous OAD in this country. So, the study was taken up to assess the pattern of ventilatory abnormality in patients with post-TB OAD and also to find out whether smoking affects the severity of airflow limitation in such patients.

MATERIALS AND METHODS

It was a cross-sectional, observational and comparative study, carried out in the pulmonary medicine OPD of V.S.S. Medical College, Burla, India, between October 2014 and September 2015. The procedures followed in this study were in accordance with the ethical standards of our Institutional Committee on human experimentation.

All adult (≥ 18 years) patients with past history of adequately treated PTB (based on history given by the patient and review of old document, whenever available), who presented to the OPD with respiratory complaints, were consecutively selected for the study. Patients with evidence of active TB (on the basis of two sputum smear for acid-fast bacilli and chest X-ray) and inadequately treated previous TB (e.g., wrong antituberculous drug regimen, inadequate dosage, incomplete course of therapy) were excluded from the study. Subjects with history of OAD or other chronic lung disease prior to TB were also excluded. HIV-positive patients were left out as HIV itself is an independent risk factor for COPD [10].

Patients who fulfilled our selection criteria were interviewed with a structured questionnaire regarding present complaints with duration, personal history (occupation, smoking etc.). Detail of past TB and its therapy was recorded according to patient's history and old documents, whenever available. "Smoker" was defined according to

Centres for Disease Control and prevention (CDC), USA guideline as the individuals who smoked at least 100 cigarettes or its equivalent in their lifetime [13]. Extent of smoking was subsequently assessed using 'Smoking Index' (SI) i.e., number of bidi or cigarette smoked per day multiplied by duration of smoking in years. Smokers were categorized as mild smoker (SI<100), moderate smoker (SI=100-300) and heavy smoker (SI>300) [14]. General survey, vital signs including saturation of oxygen measured by pulse oximetry (SpO₂) and detailed respiratory system examination findings were documented. Chest X-ray (Postero-anterior view) was done and evaluated for signs of inactive TB. Extent of lesions (pulmonary fibrosis, cavity, parenchymal calcification and bronchiectasis) in chest X-ray was assessed by two clinicians according to Willcox classification [9]. Each lung was divided into three zones in this classification and extent was described as follows:

Degree I – Minimum involvement in only one zone, without cavitation.

Degree II – Involvement of two/ three zones with/ without cavitation or involvement of one zone with cavitation.

Degree III – Severe involvement involving more than three zones with or without cavitation.

However, normal chest X-ray, pleural thickening or calcification, hyperinflation of lung or any other abnormality was categorized as "Others".

Subsequently spirometric evaluation was done by a portable spirometer, SPIROLAB II {manufactured by Medical International Research, Italy; and meets American Thoracic Society and European Respiratory Society standards (ATS & ERS)}, before and fifteen minutes after administration of 400 microgram salbutamol using pressurized metered-dose inhaler (pMDI) with small-volume spacer device. All patients were instructed not to use any bronchodilator on the preceding night and on day of procedure. Spirometric procedure was carried out as per ATS/ERS task force recommendation for standardization of lung function testing [15]. Subjects who were found to have post-bronchodilator FEV₁ (Forced Expiratory Volume in first second)/FVC (Forced Vital Capacity) <0.7 were taken up for final analysis as this value indicates the cut-off for diagnosis of OAD according to GOLD guideline. Bronchodilator Reversibility (BDR) was defined as an improvement in FEV₁ by at least 12% and 200 ml over pre-bronchodilator value. FEV₁/FVC ≥0.7 were excluded as those patients had either a normal spirometry or a purely restrictive ventilatory abnormality. Also, the individuals who failed to fulfil acceptability and reproducibility criteria of spirometry were excluded.

FEV₁, FVC, PEFR (Peak Expiratory Flow Rate) and FEF 25-75 (Mid-expiratory flow rate) were recorded for finally selected patients. Study population was divided into two groups: purely obstructive abnormality and mixed ventilatory abnormality. Purely obstructive disorder group was defined as population with FVC ≥80% whereas, OAD patients with associated FVC <80% were classified as mixed ventilatory abnormality group. Spirometric parameters were compared between these two groups. Severity of airflow limitation was assessed using post-bronchodilator FEV₁ based on latest GOLD guideline (i.e., FEV₁≥80% as mild, 80%>FEV₁≥50% as moderate, 50%>FEV₁≥30% as severe and FEV₁<30% as very severe) [10]. Spirometric parameters were also compared between smoker and non-smoker group to find out whether smoking alters the severity of airflow limitation in this study population.

STATISTICAL ANALYSIS

Data were compared for statistical significance using Fisher's-test, Chi-square test and Student's t-test, as appropriate. All analyses were performed using the IBM SPSS statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA).

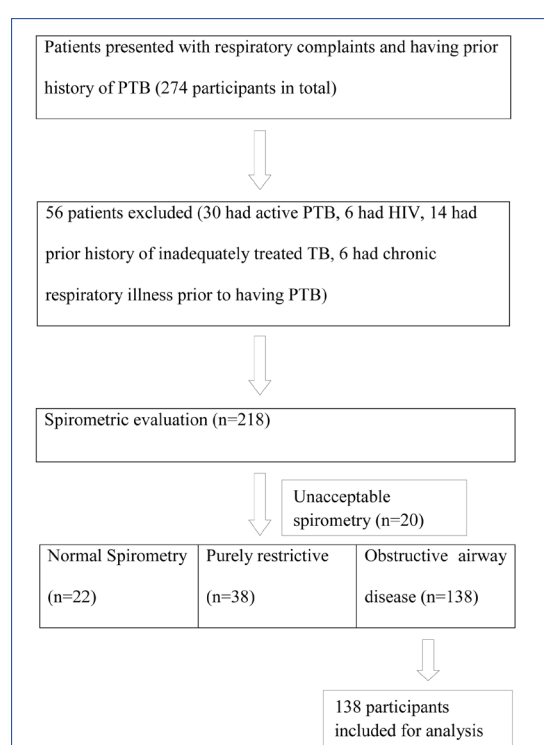
RESULTS

A total of 274 adult patients (190 male and 84 female) with prior history of PTB attended OPD with respiratory complaints within the study period. Thirty patients were excluded as they had active TB. Twenty-six more patients were excluded based on our exclusion criteria (6 had HIV, 14 had prior history of inadequately treated TB, 6 had chronic respiratory disease prior to having TB). Spirometric evaluation was done in 218 patients and out of them, 20 were excluded as their spirometry did not meet acceptability and reproducibility criteria even after repeated attempt. Twenty-two patients were found to have normal spirometric values and 38 had purely restrictive impairment [Table/Fig-1].

Therefore, a total of 138 patients were selected for final analysis. Detail of the baseline characteristics of the study population has been provided in [Table/Fig-2]. Mean age of the study population was 53.39±13.86 years. There were 60 smokers (43.48%) and 78 non-smokers in our study group. Among those 60 smokers, eight were mild smoker, 10 were moderate smoker and rest 42 were heavy smoker. A total of 33.33% of our study population (46 of 138) were farmer by occupation. Dyspnoea was found out to be the most common symptom (in 95.65% cases) followed by cough (89.85%) and expectoration (75.36%). A total of 74 of 138 patients (53.62%) developed current respiratory symptoms more than six years after the completion of their antituberculous treatment.

According to Willcox classification, Degree II was the most common radiological extent of inactive TB found in 72 out of 138 (i.e., 52.17%), followed by Degree I (24.64%) and Degree III (17.39%). Severity of airflow limitation was found to be dependent on extent of radiological lesion and this relationship was statistically significant (p<0.001, Chi-square test). It means greater degree of radiological lesion is associated with more severe airflow obstruction [Table/Fig-3]. It should also be noted that all the patients with radiological lesion of Degree III (n=24) had mixed ventilatory pattern on spirometry. On the other hand, out of all patients with pure obstruction (n=38), two had only hyperinflated lung without any fibrosis, 12 had Degree I and 24 had Degree II radiological lesion.

Hundred OAD patients had additional restrictive component as per the spirometric results and 88% of them showed poor response to short-acting bronchodilator. On the other hand, BDR was significantly greater in purely obstructive group and 22 out of 38



[Table/Fig-1]: Flow diagram of the study sample.

patients had good response to salbutamol inhalation ($p < 0.001$, Chi-square test). Regarding post-bronchodilator FEV1 (in litre) and FEV1% predicted values, patients with mixed ventilatory abnormality had significantly worse values than patients with purely obstructive disorder ($p < 0.001$, Student's t-test) [Table/Fig-4].

Smokers had a mean difference of 8.08 ± 5.70 years between completion of anti-tuberculous treatment and onset of present symptoms of OAD whereas, the difference was 9.18 ± 5.33 years in non-smokers. Although smokers apparently developed symptoms of OAD one year earlier than non-smokers, but it was not statistically significant ($p = 0.24$). No significant difference was noted in their mean SpO₂ value as well (92.63 ± 3.123 vs 92.05 ± 3.531 ; $p = 0.31$ by unpaired t-test). Post-bronchodilator percentage predicted values of FVC, FEV1, PEFr and FEF25-75 were compared between smokers and non-smokers [Table/Fig-5], but no significant difference was found for any of those parameters. We could not even demonstrate any significant difference in post-bronchodilator FEV1 among mild, moderate and heavy smokers.

Age Group (in years)	Male	Female	Total
20-29	4 (2.89%)	4 (2.89%)	8 (5.79%)
30-39	16 (11.59%)	2 (1.45%)	18 (13.04%)
40-49	16 (11.59%)	6 (4.35%)	22 (15.94%)
50-59	32 (23.19%)	2 (1.45%)	34 (24.64%)
60-69	34 (24.64%)	8 (5.79%)	42 (30.43%)
70-79	14 (10.14%)	0 (0%)	14 (10.14%)
Total	116 (84.06%)	22 (15.94%)	138 (100%)

[Table/Fig-2]: Age and sex distribution of the study population.

CXR* Lesion Extent	GOLD I (Mild)	GOLD II (Moderate)	GOLD III (Severe)	GOLD IV (Very Severe)	Total
Degree I	2	20	8	4	34
Degree II	8	30	22	12	72
Degree III	0	0	10	14	24
Others	2	2	4	0	8
Total	12	52	44	30	138

[Table/Fig-3]: Comparison of extent of radiological lesion with staging of obstructive airway disease.
*CXR: Chest X-Ray

Post-Bronchodilator	Mixed (n=100)	Obstructive (n=38)	p-value
FEV1 (L)	0.996 ± 0.328	1.475 ± 0.499	< 0.001
FEV1 % predicted	42.28 ± 14.54	67.79 ± 15.74	< 0.001

[Table/Fig-4]: Comparison of FEV1 between patients with mixed pattern and purely obstructive pattern.

Spirometric Parameters	Smokers (n=60)	Non-smokers (n=78)	p-value
FVC% predicted	72.27 ± 20.730	67.72 ± 24.117	0.245
FEV1% predicted	53.24 ± 21.107	48.43 ± 17.335	0.144
PEF% predicted	39.53 ± 15.645	36.22 ± 15.589	0.219
FEF 25-75% predicted	23.64 ± 15.831	20.37 ± 13.178	0.187

[Table/Fig-5]: Comparison of post-bronchodilator spirometric parameters among smokers and non-smokers.

DISCUSSION

Although post-TB OAD is a well-documented entity since many years, TB patients are not routinely counselled or followed up for post-tuberculous sequelae. Often such patients are wrongly treated for TB on multiple occasions on the basis of chronic cough, expectoration or haemoptysis. In the present study, we evaluated the clinical and spirometric profile of such post-TB OAD patients.

The exact pathogenesis of post-TB OAD is not clear but an immunological hypothesis has been put forward. It has also been postulated that TB causes destruction of lung parenchyma by up-regulation of different proteases and dysregulation of protease control mechanism [16]. Pulmonary damage by matrix metalloproteinase leads to cicatricial transformation of lung tissue and such fibrotic changes are probably responsible for associated restrictive disorder. Verma SK et al., in their study at Lucknow found that incidence of dyspnoea was the most common within five years of completion of anti-tuberculous treatment [8], and Rajasekaran S et al., described development of post-TB asthma within one year of completion of therapy in 50.9% of their 55 patients [17]. On the other hand, Krishna K et al., mentioned that obstructive changes were the most common after ten years of follow up [18]. Similar finding has been described by Baig IM et al., in their study among 47 post-PTB patients with chronic dyspnoea at Rawalpindi, Pakistan [19]. In our study population, more than half of the patients developed features of OAD for the first time after six years since completion of anti-TB therapy; however, possibility of recall bias cannot be excluded owing to chronicity of the OAD symptoms. As OAD can develop anytime during the course of PTB or even after successful completion of antituberculous therapy, it can be logically said that prevalence of OAD increases with number of years passed since successful treatment of TB [20].

We observed predominantly mixed pattern of spirometric abnormality in the study population and such fact may be supported by results of several other studies [21-23]. Such a high prevalence of mixed pattern can be explained by the extensive fibrosis co-existing with airflow obstruction. This sort of fibrotic sequelae is quite common in India as people often present to health facility late in course of their TB owing to poor socio-economic condition. Verma SK et al., described similar findings in their study among 92 post-PTB individuals and they found restrictive pathology in 37 and mixed pattern in 21 patients as per spirometric criteria [8]. However, 55.3% of post-PTB chronic dyspnoea cases ($n = 47$) had obstructive ventilatory disorder without any restrictive component in above mentioned Rawalpindi study [19]. Also, most of the patients with mixed spirometric pattern in our study showed poor BDR which may indicate that cicatricial fibrosis is a hindrance to bronchodilatory effect of salbutamol. But, Verma SK et al., did not describe any significant difference in BDR between purely obstructive and mixed disorder group [8].

It had been documented that PTB occurred more commonly among smokers since long. Probably this is due to the fact that nicotine turns off Tumour Necrosis Factor-alpha (TNF- α) production by the lung macrophages, thereby making the patient more susceptible to the development of progressive disease from latent *Mycobacterium tuberculosis* infection [24]. But regarding post-TB OAD, present study failed to establish any relation between smoking and severity of airflow limitation. Similar finding was also described by Ramos LM et al., Di Naso et al., Singla et al., and Lam KB cohort study [21-23,25]. A strong association between a medical history of TB and airflow obstruction has been proved beyond doubt by a large, population based, multicentre study in Latin America (PLATINO study) [26]. However, no definite hypothesis has been put forward to explain such findings in above mentioned studies. Possibly, in country like India, people are exposed to many risk factors for COPD apart from smoking; like indoor or outdoor air pollution, occupational exposure to dust/smoke which might have played a role of confounding factors among non-smoker patients in this study, thereby diluting the overall effect of tobacco smoking.

LIMITATION

Present study involved only one tertiary care hospital and had a relatively small study sample. We have included only symptomatic patients in our study. Thereby all asymptomatic patients were left out who might have spirometric features of pulmonary function

impairment. In this study, “smoker” group included both current and ex-smokers. Presence of subjects who stopped smoking several years ago in the “smoker” group might be a confounding factor in comparison between smoker and non-smoker group.

Post-TB patients with normal spirometry or only restrictive impairment were not evaluated in our study. So, the actual scenario of post-TB pulmonary impairment could not be assessed. Also, total lung volume estimation by body plethysmography was not done due to lack of facility. Therefore, it could not be confirmed whether some patients with severe obstructive disorder had been misclassified as mixed spirometric abnormality.

CONCLUSION

Such pulmonary function impairment after treatment of TB is still a less recognized cause of chronic lung disease worldwide. Physicians should be aware of the long-term risk of developing airflow limitation in individuals with prior TB, irrespective of smoking status. Such patients commonly have additional restrictive ventilatory disorder, which further complicates the issue. Proper counselling to PTB patients and regular follow up even after completion of anti-TB therapy is absolutely essential to detect post-TB OAD at its earliest as it may develop anytime during or after TB treatment. Periodic spirometry may be beneficial to detect pulmonary impairment early in its course. Finally, it can also be said that early diagnosis and appropriate treatment of PTB is important to minimize post-TB fibrosis which may complicate post-TB OAD by worsening overall lung function.

REFERENCES

- [1] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006; 367:1747–57.
- [2] Ehrlich R, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Wheeze, asthma diagnosis and medication use: a national adult survey in a developing country. *Thorax*. 2005; 60:895–901.
- [3] Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax*. 2000;55:32–8.
- [4] Murray J, Kielkowski D, Reid P. Occupational disease trends in black South African gold miners. An autopsy-based study. *Am J Respir Crit Care Med*. 1996;153:706–10.
- [5] Lee JH, Chang JH. Lung function in patients with chronic airflow obstruction due to tuberculous destroyed lung. *Respir Med*. 2003;97:1237–42.
- [6] Leung CC, Chang KC, Law WS, Yew WW, Tam CM, Chan CK, et al. Determinants of spirometric abnormalities among silicotic patients in HongKong. *Occup Med (Lond)*. 2005;55:490–93.
- [7] Mohan A, Premanand R, Reddy LN, Rao MH, Sharma SK, Kamity R, et al. Clinical presentation and predictors of outcome in patients with severe acute exacerbation of chronic obstructive pulmonary disease requiring admission to intensive care unit. *BMC Pulm Med*. 2006;6:27.
- [8] Verma SK, Narayan KV, Kumar S. A study on prevalence of obstructive airway disease among post pulmonary tuberculosis patients. *Pulmon*. 2009;11:4-7.
- [9] Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med*. 1989;83:195-98.
- [10] Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, updated 2016. pp. 6. Available from: <http://goldcopd.org/>.
- [11] Snider GL, Doctor L, Demas TA, Shaw AR. Obstructive airway disease in patients with treated pulmonary tuberculosis. *Am Rev Respir Dis*. 1971;103:625-40.
- [12] Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al. Pulmonary impairment after tuberculosis. *Chest*. 2007;131:1817-24.
- [13] Centers for Disease Control and Prevention. Cigarette smoking among adults and trends in smoking cessation - United States, 2008. *MMWR*. 2009;58:1227-32.
- [14] Jindal SK, Malik SK. Smoking index - a measure to quantify cumulative smoking exposure. *Lung India*. 1988;6:195-96.
- [15] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:153-61.
- [16] Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. *J Infect Dis*. 2005;192:1201–09.
- [17] Rajasekaran S, Savithri S, Jeyaganesh D. Post-tuberculosis bronchial asthma. *Ind J Tub*. 2001;48:139-42.
- [18] Krishna K, Bond S, Artvinli M, Reid KDG, McHardy GJR, Crofton JW. Pulmonary function in treated tuberculosis; a long term follow-up. *Am Rev Respir Dis*. 1977;115:402-04.
- [19] Baig IM, Saeed W, Khalil KF. Post-tuberculous chronic obstructive pulmonary disease. *J Coll Physicians Surg Pak*. 2010;20:542-44.
- [20] Chest Research Foundation. *Respi Mirror*. Volume I, Issue 1, October 2011. History of TB? Check for OAD. Pune, India: Chest Research Foundation. pp. 1-2.
- [21] Ramos LM, Sulmonett N, Ferreira CS, Henriques JF, de Miranda SS. Functional profile of patients with tuberculosis sequelae in a university hospital. *J Bras Pneumol*. 2006;32:43-7.
- [22] Di Naso FC, Pereira JS, Schuh SJ, Unis G. Functional evaluation in patients with pulmonary tuberculosis sequelae. *Rev Port Pneumol*. 2011;17:216-21.
- [23] Singla N, Singla R, Fernandes S, Behera D. Post treatment sequelae of multi-drug resistant tuberculosis patients. *Indian J Tuberc*. 2009;56:206-12.
- [24] Davies PD, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, et al. Smoking and tuberculosis: the epidemiological association and immunopathogenesis. *Trans R Soc Trop Med Hyg*. 2006;100:291-98.
- [25] Lam KB, Jiang CQ, Jordan RE, Miller MR, Zhang WS, Cheng KK, et al. Prior TB, smoking, and airflow obstruction: a cross-sectional analysis of the Guangzhou Biobank cohort study. *Chest*. 2010;137:593–600.
- [26] Menezes AMB, Hallal PC, Perez-padilla R, Jardim JRB, Muino A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J*. 2007;30:1-6.

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