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Original Research Article

Presentation of pulmonary tuberculosis in diabetics and response to anti-tuberculosis therapy

Md Abdul Waseem[1]*, Misba Zahera[2], V. Gopalakrishnaiah[3]

[1]Department of Pulmonary Medicine, Osmania Medical College, Hyderabad, Telangana, India
[2]Civil Assistant Surgeon, Government of Telangana, Karimnagar, Telangana, India
[3]Department of Pulmonary Medicine, Bhaskar Medical College, Hyderabad, Telangana, India

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***Correspondence:**
Dr. Md Abdul Waseem,
E-mail: waseemz82704@gmail.com

ABSTRACT

Background: Diabetes and Tuberculosis are known to be mutually affective. In high tuberculosis and Diabetes burden country like ours, it is essential that we understand all the aspects concerning both these diseases individually and in mutual coexistence, in order to improve the management of this unhealthy partnership.
Methods: This is a prospective hospital based observational study, in which 100 patients with coexisting Diabetes and new sputum confirmed pulmonary tuberculosis with no other comorbidities were included. Detailed history, examination and appropriate investigations were done evaluating the clinical and radiological presentation and treatment response in terms of sputum conversion at follow up visits.
Results: Predominant symptoms were anorexia, fever and cough with sputum, majority with duration of more than 4 weeks. About half of them had diabetes duration of less than 1 year, most being newly diagnosed. All cases had upper lobe involvement; two thirds of them had lower lung field and multiple lobe involvement. Confluent consolidation, cavitary lesions and fluffy infiltrates were common. 27 of the 100 cases had a delayed sputum conversion. Longer duration of diabetes, maintenance on oral hypoglycaemic drugs alone and uncontrolled diabetes had delayed sputum conversion.
Conclusions: Presenting symptoms of tuberculosis in diabetics is more or less similar to that in non-diabetics. Atypical radiological presentation with lower lung field involvement and confluent consolidation mimicking pneumonia is common. Delay in sputum conversion is common in dual disease and is increased with increasing DM duration and poor glycemic control. Better results may be obtained with insulin therapy.

Keywords: Diabetes, DOTS, Glycated haemoglobin, Sputum conversion, Tuberculosis

INTRODUCTION

Tuberculosis is one of the top 10 causes of death worldwide. 10.4 million people fell ill with TB, out of whom 1.8 million people died in 2015. 60% of the cases occurred in only six countries, which included India. In 2014, 422 million people in the world had diabetes-a prevalence of 8.5% among the adult population, of which 96 million belong to the South-East Asia region. Diabetes caused 1.5 million deaths in 2012. Prevalence of diabetes in India is 7.8%. Diabetes mellitus is increasing globally and in India.[1,2] Avicenna noticed the association between tuberculosis and diabetes more than thousand years ago. More than a hundred years ago, half of diabetic patients who died were found on post-mortem to be suffering from pulmonary tuberculosis. In a study in Mumbai, India, tuberculosis was found to be the most common complicating illness among diabetics (5.9%) in a large cohort study of over 8000 patients with diabetes mellitus.[3] The recent studies predict that in India 18.4% (12.5% to 29.9%) of people with pulmonary tuberculosis (both smear-positive and smear-negative) have diabetes

and that in the smear-positive group diabetes prevalence is 23.5% (12.1-44%).[4] Many immunologic abnormalities and physiological dysfunctions have been described in diabetes (Table 1).

Table 1: List of defects in diabetics' immunologic make- up and physiologic pulmonary functions.

Immunologic abnormalities in diabetics	Pulmonary physiologic dysfunctions in diabetics
Abnormal chemotaxis, adherence, phagocytosis and microbicidal function of polymorphonuclear cells.	Diminished bronchial reactivity.
Decreased peripheral monocytes with impaired phagocytosis.	Reduced elastic recoil and lung volumes.
Poor blast transformation of lymphocytes.	Reduced diffusion capacity
Defective C3 opsonic function	Occult mucus plugging of airways

Taking into consideration this link between diabetes mellitus and tuberculosis on one hand and the current epidemic of diabetes mellitus in both the developing as well as the developed countries on the other hand, we can propose the size of this health problem.

Studies conducted after the introduction of the glucose tolerance test in the 1950s, have shown high prevalence of impaired glucose tolerance in patients with tuberculosis with rates ranging from 2-41%. There have been reports of high prevalence rates of diabetes in cases of pulmonary tuberculosis (4-20%) and rates are higher for impaired glucose tolerance test (16-29%). After anti-tuberculous therapy, 50% of them had normalization of glucose intolerance. Some investigators have reported an association between severity of tuberculosis and abnormal glucose tolerance test.[5,6]

The aim of the study was to evaluate the clinical and radiological presentation of tuberculosis in diabetic patients. And to note the response to treatment, especially with respect to sputum conversion in relation to DM duration, DM treatment (OHA/ Insulin) and glycemic control (HbA1C).

METHODS

This is a prospective hospital based observational study, in which 100 patients in the age group 30 to 75 years with coexisting Diabetes mellitus type 2 and new cases of sputum acid fast bacilli positive pulmonary tuberculosis attending Bhaskar hospital between January and December 2016 were included. Informed consent was taken from all the patients and also permission was obtained from the institutional ethics committee. Immunocompromised patients with HIV, on steroids, renal or hepatic diseases were excluded. Patients on thiazide diuretics, previously diagnosed TB cases and smear AFB negative cases were also excluded. All the participating patients were asked by a detailed questionnaire about their personal information, history of present symptoms, diabetes history and medications taken, any significant past history. All the patients were systematically examined thoroughly. All patients were sent for sputum smear examination, fasting blood glucose, postprandial glucose, glycated hemoglobin (HbA1C- Electrophoresis method), chest x-ray PA view, complete blood picture and renal and liver function tests. Two sputum samples, one preferably collected in the early morning, were subjected to fluorescent staining with auramine-O stain at the designated microscopy center (under RNTCP) at our institute. Sputum smear positivity was graded as per RNTCP guidelines.

Culture was done with Lowenstein Jensen medium. Pulmonary tuberculosis was treated with Category 1 short course DOTS therapy as per RNTCP. Extension of DOTS therapy was done in patients who failed sputum conversion at 2 months of therapy.

Diabetes was diagnosed as per American diabetes association criteria (Table 2) and was managed with oral hypoglycemic agents with or without insulin, so as to maintain a strict glycemic control.

Table 2: Diagnosis of diabetes mellitus as per American diabetes association.

Diagnosis of diabetes mellitus
FPG ≥126 mg/dl (7.0mmol/l). fasting is defined as no caloric intake for at least 8 hours. Or
2-h PG ≥200 mg/dl (11.1mmol/l) during an OGTT. the test should be performed as described by the who, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.* Or
a1c ≥6.5% (48mmol/mol). the test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.* Or
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1mmol/l).

All patients were followed up at 2 months, 3 months and at the end of treatment. During each follow, up they were asked about their symptoms and any complications or issues related to the treatment. They were thoroughly examined systematically and underwent sputum smear examination, AFB culture, chest x-ray PA view, fasting and post-prandial blood sugar values, Glycated hemoglobin if required, complete blood picture, renal and liver function tests.

RESULTS

This study revealed male to female ratio of 2.3:1. Predominant symptoms were anorexia, fever and cough with sputum. 67 patients had a symptom duration of >4 weeks. 50 patients had a glycated hemoglobin level

between 8 and 10, 23 patients had between 6.5 and 7.9, 20 patients had levels more than 10 and 7 patients had levels between 4.0 and 6.5. Mean glycated hemoglobin level was 7.9, ranging between 6 and 10.8.

All 100 patients had upper lobe involvement, 70 patients had lower lung field involvement, 70 patients had multiple lobe involvement and 36 patients had bilateral involvement.

Cavitary lesions are seen in 46 patients, infiltrates or cotton wool type of opacities are seen in 46 patients, consolidation is seen in 56 patients, pneumothorax is seen in 12 patients and pleural effusion is seen in 3 patients (Figure 1).

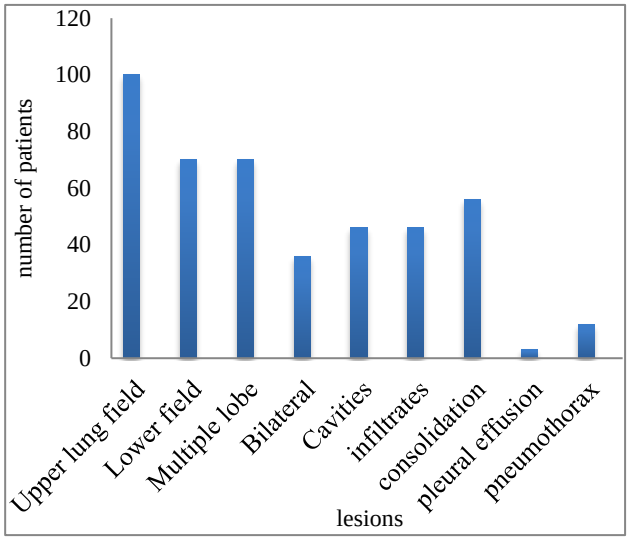

Figure 1: Radiological findings.

43 patients had a sputum AFB load of less than or equal to 1+ (including culture positive), 40 patients had a sputum AFB of 2+ and 17 patients had a level of 3+ (Table 3).

Table 3: Sputum for acid-fast bacilli, fluorescent staining.

Sputum AFB	Number of cases
</= 1+	43
2+	40
3+	17

73 patients had their sputum AFB conversion to negative after 2 months of treatment and 27 patients had sputum conversion at 3 months of treatment. Out of 76 cases on OHA, 52 had sputum conversion at 2 months and 24 cases converted to sputum negative at 3 months.

Out of the 20 cases on OHA and insulin 17 cases converted at 2 months and 3 cases converted at 3 months. Four cases, which were on insulin alone, converted at 2 months (Table 4).

Table 4: Distribution of sputum conversion according to diabetes treatment.

Diabetes treatment	Total cases	Conversion at 2months	Conversion at 3months
OHA	76	52 (68%)	24 (32%)
Insulin	4	4 (100%)	0
OHA+ insulin	20	17 (85%)	3 (15%)
Total	100	73	27

Out of the 76 cases that had diabetes duration of 0-5 years, 66 cases (87%) converted to sputum negative at 2 months and 10 cases (13%) converted at 3 months. Out of the 24 cases with diabetes duration of 6-10 years, 16 cases (67%) converted at 3 months and 8 cases (33%) converted at 2 months (Graph 2).

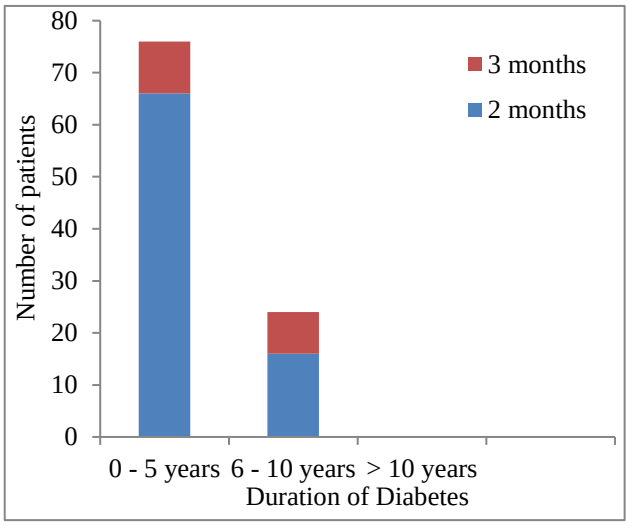

Figure 2: Smear conversion according to duration of diabetes.

7 cases of the 23 cases who had a HbA1C level of 7.1 to 7.9 had a sputum AFB conversion at 3 months of ATT. 17 cases out of 50 with a HbA1C level of 8 to 10 had sputum AFB conversion at 3 months of ATT. 4 cases with a HbA1C level more than 10 converted at 3 months of ATT (Graph 3).

Ninety cases completed the ATT and were cured, 8 cases were lost to follow up and two patients died due to cardiorespiratory failure. Standard duration of ATT (DOTS) was given in 53 cases. Extended therapy of more than 6 months was required in 37 cases. Of them 27 cases had delayed sputum conversion earlier (at 3 months) and 10 cases were extended therapy in view of persistent lesions radiologically.

DISCUSSION

In this study there was a clear male predominance, which correlated with most of the studies.[7-9]

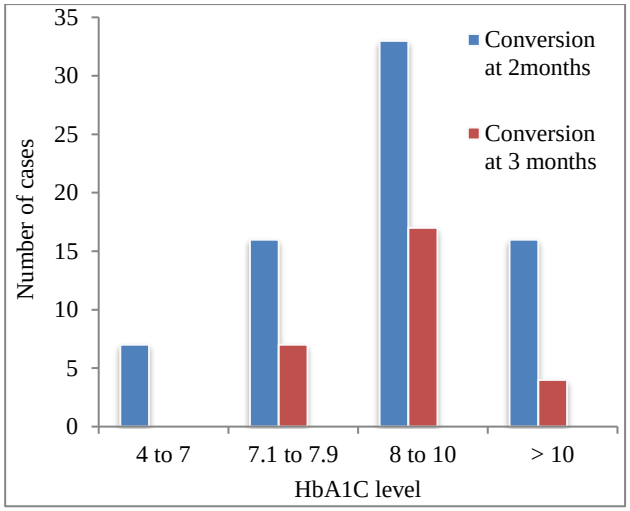

Figure 3: Sputum AFB conversion according to Glycated hemoglobin level.

The high incidence of disease in males is possibly due to the fact that both tuberculosis and diabetes are more common in males. Another reason could be that the number of male patients attending the hospital is more than females. Predominant symptoms were more or less similar to that in non-diabetics. Most of the studies also showed no much difference in symptomatology.[10-12]

This study showed about half the cases with diabetes duration of less than 1 year, majority of them being diagnosed de novo, before the start of tuberculosis treatment. The reason for this may be drawn from the hypothesis that latent diabetes may be unmasked by active pulmonary tuberculosis.[13] In a study from Tanzania, 73% and 61% of diabetics, respectively, were newly diagnosed concurrent with active TB.[14]

Majority of the patients had mild to moderate hyperglycemia rather than severe hyperglycemia which suggests development of glucose intolerance due to tuberculosis, thereby stressing on the need to screen tuberculosis cases for diabetes before the start of anti-tubercular therapy, so that hyperglycemia may be controlled which has an overall positive impact on TB treatment itself. This finding correlate with studies by Jeon CY and others and Deshmukh PA.[7,15]

A social business model developed and implemented by an international NGO in Bangladesh and Pakistan incorporated active screening for TB in private clinics, private hospitals and laboratories. TB screening in private clinics in the megacity of Karachi doubled the case notifications from the city in a year; also, over 2000 additional TB cases were detected by the project site in Dhaka in a year.[16]

More than two thirds of our cases had a glycated hemoglobin value of more than 8%. This suggests that uncontrolled diabetes is strongly associated with tuberculosis and the need to monitor HbA1C levels during treatment of tuberculosis so as to maintain a strict diabetes control. These findings correlate with the study Chi C. Leung and others.[17]

The chest x-ray in our study had increased lower lung field, multiple lobe and bilateral involvement. In many comparative studies, chest X-ray images from patients having tuberculosis with diabetes mellitus have been described as 'atypical', mainly because they frequently involve the lower lung fields, often with cavities.[10,18,19]

Pulmonary tuberculosis is found predominantly in the upper lobes. Lower lung field tuberculosis occurs but is often misdiagnosed as pneumonia, carcinoma or lung abscesses.[12] The radiological aspects of concomitant tuberculosis and diabetes were first described by Sosman and Steidl.

They reported that "diabetic tuberculosis" has a special radiological pattern consisting of confluent, cavitary, and wedge-shaped lesions spreading from the hilum towards the periphery, predominantly in lower zones.[20] According to many studies, it seems that cavitary lesions are more common among diabetic patients, especially cavitary nodular lesions.[19,21]

In this study, there was an increase in the time taken for sputum conversion in a significant number of patients. According to studies, the time taken for sputum conversion to negative is longer in patients with coexisting diabetes and it improves when the intensive phase of treatment is prolonged by 1 month.[22,23]

This observation also signifies that treatment strategy of prolonging the intensive phase of treatment by 1 month in patients who remain smear positive at the end of 2 months, as suggested by the WHO guidelines, may also be valid for diabetic patients. In a systematic review by Baker et al., 8 out of 9 studies reported delayed sputum culture conversion. Also 5 of these studies showed a relative risk of more than 2 and 3 of them showed a RR of less than one.[24]

Tuberculosis worsens glycemic control and makes the control of diabetes difficult.[25,26] Maintenance of blood sugar level at normal or near normal level is one of the most fundamental aspects in patient care. Whether this aggressive control of hyperglycemia should be done only with oral hypoglycemic agents or whether the use of insulin is mandatory is still an area of uncertainty. Insulin is clearly the preferred agent of choice in Diabetes with TB.

In a study by Park SW, uncontrolled diabetes was shown to be a significant risk factor for a positive sputum culture at 2 months (odds ratio, 4.316; 95% CI, 1.306-14.267; p=0.017). Also, uncontrolled diabetics seem to have more cavities, higher positive smear rates and lack of culture conversion after two months of therapy.[27]

CONCLUSION

Presenting symptoms of tuberculosis in diabetics is more or less similar to that in non-diabetics. Atypical radiological presentation with lower lung field involvement and confluent consolidation mimicking pneumonia is common. Active tuberculosis alters blood glucose control, thereby unmasking latent diabetes. Hence, higher index of suspicion is required in detecting tuberculosis in diabetics and vice versa and it is appropriate to actively screen for DM in patients with TB. Delay in sputum conversion is common in dual disease and is related to DM duration, DM treatment and glycemic control (HbA1C). Although standard duration of therapy is sufficient in most cases, an extension may be needed in a significant number. Control of blood sugars should be the ultimate aim and the treatment should be individualized. However, this study shows better results with the use of insulin.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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