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Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

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Vol. 38, No. 2, July 2014

ORIGINAL ARTICLE

"Bronchoprovocation Test by Inhaled Dry Powder Mannitol for Airway Hyper responsiveness and Comparison of its Safety and Efficacy with Hypertonic Saline and Methacholine"

S M Lutfor Rahman[1], Bashir Ahmed[2], Md. Naimul Hoque[2], Md. Abdur Rouf[2] Mohammed Shahedur Rahman Khan[2], Md. Abu Raihan[2], Md. Khairul Hassan Jessy[2], Habib Uddin Ahmad[1], Md. Aminul Islam[5], Rustom Ali[3], Md. Rashidul Hassan[4]

Abstract:

Introduction: *Inhaled mannitol is a new bronchial provocation test (BPT) developed to improve portability and standardization of osmotic challenge testing. Osmotic challenge tests have an advantage over the traditional methods of measuring airway hyper responsiveness using methacholine as they demonstrate higher specificity to identify bronchial hyper responsiveness. The safety and the efficacy of mannitol as a BPT to measure airway hyper responsiveness were compared to hypertonic saline and methacholine (as gold standard) in people both with and without signs and symptoms of asthma.*

Methods: *A double blind, randomized, crossover study was carried out in asthmatic and non-asthmatic subjects. A total of 118 subjects were recruited and 107 subjects completed at least the two studies (Mannitol and Hypertonic saline) and 75 subjects completed all three studies. Mannitol was delivered using a low resistance dry powder inhaler device; hypertonic saline and methacholine delivered using a nebulizer. The FEV_1 was measured 60 seconds after each dose of mannitol (5, 10, 20, 40, 80, 160, 160, 160mg) and after each exposure to hypertonic saline (4.5%, 9.0%, 13.5% and 18.0%) and methacholine (0.025, 0.25, 2.5, and 10.0 mg/ml). A 15% fall in FEV_1 (PD15) defined a positive test for mannitol or hypertonic saline (HS) and 20.0% fall in FEV_1 (PC20) for methacholine (Anderson et al. 1997). Each challenge was performed at least one week apart. Adverse events were monitored and diaries kept for 7 days following the tests for monitoring the adverse events.*

Results: *The mean ages were 34.52±10.37 years and 34.15±9.45 years in asthmatic patients and non-asthmatic subjects respectively, which was almost similar between two groups. Majority of the study subjects belonged to 31 - 40 years of age group in both groups that was 35.7% in asthmatic patients and 33.3% in non-asthmatic subjects. Male was predominant in both group, which was 51.79% and 52.94% in asthmatic and non-asthmatic subjects respectively and male female*

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ratio was 1.1:1 in the whole study. Mean pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate and SpO_2 (Oxygen saturation) were almost similar, at baseline, after test and at follow up between two groups. In this study, it was found that Methacholine bronchoprovocation test was highly sensitive (98.0%) but less Specific (76.0%), however Mannitol and Hypertonic saline bronchoprovocation test was highly Specific (98.0% in Mannitol and 96.0% in Hypertonic saline) but less sensitive (71.0% Mannitol and 75.0% in Hypertonic saline). No serious adverse events were recorded.

Conclusion: *The efficacy and safety of mannitol was demonstrated in non-asthmatic and clinically diagnosed asthmatic patients. The mannitol challenge was generally safe and well tolerated. No serious adverse events were recorded and it is easier to perform, tasteless as well as convenient for the patients, so mannitol bronchoprovocation test is now preferred.*

Key words: *Bronchoprovocation test, Mannitol, Hypertentonic saline, Methacholine.*

[Chest & Heart Journal 2014; 38(2) : 67-79]

Introduction:

Asthma is one of the most common chronic inflammatory disorders of the airways with significant morbidity and mortality. Around 300 million people in the world currently have asthma. It is estimated that there may be an additional 100 million people with asthma by 2025.[1]

According to First National Asthma Prevalence Study (NAPS) 1999, in Bangladesh about 7 million people (5.2% of population) are suffering from current asthma (at least three episodes of asthma attack in last 12 months).

The disease causes physical, emotional and financial suffering for patients and families and a socio-economic burden to the country. Asthma accounts for about 1 in every 250 deaths worldwide, although 80% of such deaths are preventable with modern management of asthma. Diagnosis of asthma is based on clinical findings along with an objective test.

Asthma is easy to diagnose and equally easy to miss specially in some special varieties, like cough variant asthma. To diagnose this use of histamine and methacholine bronchoprovocation test is well established for identifying airway hyper responsiveness (AHR) but the AHR to these agents is not specific for asthma diagnosis.[2]

In 1981 it was reported that the airways of asthmatic patients narrowed in response to the inhalation of nonisotonic aerosols of sodium chloride.[3] This finding was later confirmed and extended to show that increasing airway osmolarity with dextrose rather than sodium chloride also provoked airway narrowing in asthmatic individuals.[4] Subsequently, a BPT with hypertonic (4.5%) saline was developed and standardized for use in adults and children.[5] Hypertonic saline has been used to assess the acute and chronic effect of drugs employed in treating asthma.[6] The stimulus and mechanism whereby hypertonic saline causes airway narrowing is thought to respectively involve an increase in osmolarity and release of mediators from mast cells and sensory nerves.[7] Antihistamines given both orally.[8] and by aerosol [9] markedly reduce the airway response to hypertonic saline. In vitro, the human lung mast cell releases histamine in response to an increase in osmolarity.[10] At the same osmolarity, mannitol is more potent than sodium chloride in causing this release of mast-cell histamine.[11] Moreover mannitol is an inert substance, tasteless, easy to performed and safe as well as cheap.

The mannitol BCT provides a standardised and rapid point-of-need test to identify currently active asthma, and is clinically useful in the identification of patients with asthma who are likely to benefit from inhaled corticosteroid therapy.[13]

Therefore we investigated the effect of inhaled mannitol from a dry powder inhaler both in asthmatic and non-asthmatic subjects and compared it to hypertonic saline and methacholine

delivered by a nebulizer. The response of mannitol as a BPT was measured as well as adverse effects were noted and compared with those of inhaled methacholine and hypertonic saline.

Long-term aim of our study was the use of the dry powder preparation of mannitol for BPT for diagnosing and assessing the severity of airway hyper responsiveness, and for assessing the effects of medication used in the treatment of asthma.

Materials and Methods:

This was a double blind randomized crossover study, performed during the one year period from February 2010 to January 2011, at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.

Subjects with bronchial asthma fulfilling the inclusion and exclusion criteria were selected as cases and non asthmatic individuals as controls.

A total of 118 subjects were recruited after taking informed consent to participate in this study and 107 subjects completed at least the two studies (Mannitol and Hypertonic saline) and 75 subjects completed all three studies (Mannitol, Hypertonic saline and methacholine bronchoprovocation test). Those 107 subjects who completed at least the two studies were divided into two groups (56 cases and 51 controls), 75 subjects who completed three challenges were included in the population that could be analyzed for comparison with gold slandered (Methacholine), by random sampling method 10- 50 years of ages, of both sexes, non smoker asthmatic subjects those have active symptoms and signs of mild to moderate asthma according to the Expert panel report 2 criteria. The non asthmatic subjects never had a clinical diagnosis of asthma or experienced symptoms and signs of asthma for control group. Subjects have a base line FEV_1 >70% of normal predicted values for asthmatic subjects or >80% of normal predicted values for non-asthmatic subjects. Persons able to perform repeatable spirometry according to the American Thoracic society (ATS) criteria and gave consent were included in the study.

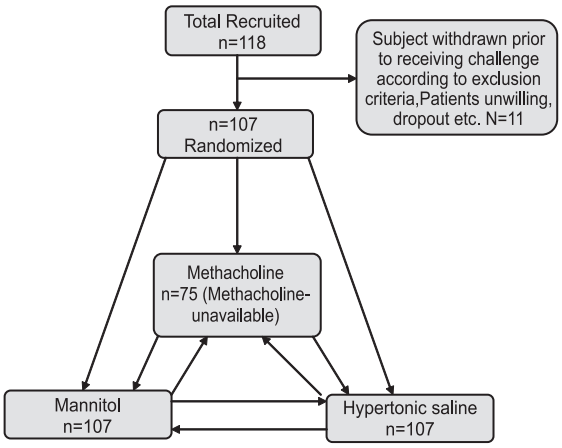
Persons <10 and > 50 years of age, smokers, subjects having active upper or lower respiratory tract infection severe enough to require a medical consultation or any other acute or chronic pulmonary disorder including Chronic Obstructive Pulmonary Disease (COPD), Bronchiectasis, Tuberculosis, Lung cancer, Cystic Fibrosis, subjects with current uncontrolled hypertension or known aortic aneurism, myocardial infarction or cerebral vascular accident in the last 6 months or ocular or abdominal surgery in the last 3 months, were excluded from the study. Breast feeding or pregnant lady and persons having a known intolerance to mannitol or salbutamol or hypertonic saline were also excluded from the study.

Mannitol was delivered using a low resistance dry powder inhaler device; hypertonic saline and methacholine delivered using a nebulizer.

At first visit, every individual underwent the first challenge accordingly. The second and third challenge were scheduled at least one week later for each challenge at second or third visit and the study was completed a week after the third challenge. The second and third challenge was selected alternatively one after another. The FEV_1 was measured 60 seconds after each dose of mannitol (0, 5, 10, 20, 40, 80, 160, 160, 160 mg), after each exposure to HS (4.5, 9.0, 13.5 and 18.0%) and each dose of Methacholine (0.025, 0.25, 2.5, 10.0 (mg/ml). In every concentration two reproducible spirometry reading were taken and highest one was selected. Each challenge was performed at least one week apart for providing proper washout time and watching the adverse effect through the week.

The respiratory technician conducting the initial challenge was blinded to the subject's asthma status and the respiratory technician conducting the reciprocal challenge was blinded to the results of the initial challenge and the asthma status of the subject. The investigator was blinded to the results of all challenge and results were collected by the investigator at the end of each week.

Each subject was issued with a study diary at first visit and requested to complete the diary every day up to their last visit when they handed it to the investigator. The diary was a record of adverse events, respiratory symptoms and concomitant medications. The investigator was responsible for



Flow chart showing the progression of subjects through the study.

reviewing the diary for completeness at the final visit.

Calculation of responses

The highest value of 2 repeatable FEV_1 measurements made after each dose was used in the calculation for the % fall in FEV_1. The dose of mannitol (mg) or saline (%) to provoke a 15.0% fall in FEV_1 (Pd15) or Methacholine 20.0% (Pc20) was calculated by linear interpolation from the curve relating the % fall in FEV_1. For mannitol this was from the post 0 mg capsule baseline value for FEV_1 to the cumulative dose of mannitol delivered (e.g. 5 mg, 15 mg, 35 mg, 75 mg, 155 mg, 315 mg, 475 mg, and 635 mg). For saline this was from the post 0.9% NaCl nebulization baseline value for FEV_1 to the maximum percentage dose of hypertonic saline delivered (4.5%, 9.0%, 13.5% and 18.0%). The dose was expressed as % used. For Methacholine this was from the post 0.9% NaCl nebulization baseline value for FEV_1 to the maximum dose of methacholine (0.025, 0.25, 2.5, 10 mg/ml) delivered

Efficacy was analyzed using sensitivity and specificity of the mannitol challenge with respect to the hypertonic saline and Methacholine challenge and the clinical assessment. Subjects were considered positive to a test if at least a 15% (for Mannitol and Hypertonic saline) or 20.0% (Methacholine) reduction in FEV_1 from baseline occurred. Subjects who reached the end of a challenge with <15% reduction in FEV_1 were considered to have a negative response.

Statistical methods

The sample size of 107 was primarily based on safety and chosen to be large enough to document the adverse event profile of dry powder mannitol. To compare the adverse events for mannitol, HS and Methacholine 2 × 2 contingency tables were used. Efficacy was analyzed in terms of response to each challenge (Mannitol and HS) those who had completed both Mannitol and HS challenge and Mannitol, HS and Methacholine in subjects who had completed mannitol, HS and Methacholine challenges.

Cross-tabulations were performed to create 2 × 2 tables of the number of subjects within each of four cells for each challenge. In the analysis of mannitol vs. HS, the four cells comprised of those positive to both challenges, those negative to both challenges, those positive to mannitol and negative to HS, and those negative to mannitol and positive to HS. Sensitivity was calculated as the probability of a positive test result with mannitol, given a positive HS result, i.e. the number of subjects positive to mannitol out of the total number of subjects positive to HS. Specificity was calculated as the probability of a negative test result with mannitol, given a negative HS result, i.e. the number of subjects negative to mannitol out of the total number of subjects negative to HS. Similar analysis was performed for mannitol vs. Methacholine and HS vs. Methacholine. Similar analysis was performed for mannitol vs. hypertonic saline.

Statistical analysis was performed using SPSS 16.0 programmed. Data were defined as means ± standard deviation. Student t-test and Chi-square tests were used where appropriate. P values <0.05 was considered to be statistically significant.

Observations and Results:

A total of 118 subjects were included in this study, out of which 107 subjects of 15 to 50 years of age were completed two challenge (Mannitol and Hypertonic saline bronchoprovocation test), 75 completed three (Mannitol, Hypertonic saline and methacholine bronchoprovocation test) challenge and were included in the population that could be analyzed for comparison with gold slandered (Methacholine).

Table-I

Age distribution of the study patients in years (n=107)

Age in years	Asthmatic (n=56)		Non Asthmatic (n=51)		P Value
	n	%	n	%	
15-20	7	12.50	6	11.77	
21-30	16	28.57	14	27.45	
31-40	20	35.71	17	33.33	
41-50	13	23.22	14	27.45	
Mean±SD	34.52	±10.37	34.15	±9.45	0.728^{ns}
Range (Min -Max)	(15	-60)	(18	-58)	

NS= Not significant
P value reached from unpaired t-test

This study was conducted among 107 patients and they were divided into five age groups. The mean±SD age were 34.52±10.37 years range from 15 to 50 years in asthmatic patients and 34.15±9.45 years range from 18 to 50 years in non-asthmatic patients. Mean age difference was not significant (p>0.05) in unpaired t-test.

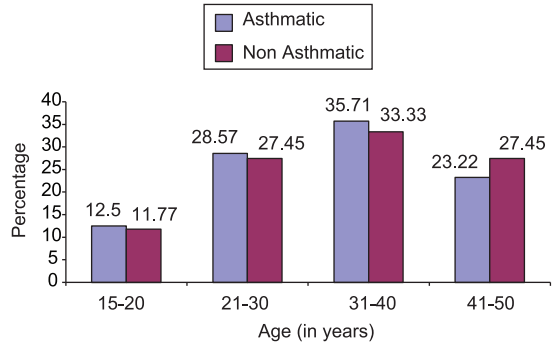


Fig.-1: *Age distribution of the study patients in years.*

Table-II

Sex distribution of the study patients (n=107)

Sex	Asthmatic (n=56)		Non Asthmatic (n=51)		P Value
	n	%	n	%	
Male	29	51.79	27	52.94	0.717^{ns}
Female	27	48.21	24	47.06	

NS=Not significant
P value reached from chi square test

Table II shows the sex distribution of the study patients and observed that, most 29(51.79%) and 27(52.94%) of the study patients were male in asthmatic and non-asthmatic patients respectively. Male female ratio was 1.1:1 in the whole study. No significant (p>0.05) difference was observe in Chi square test.

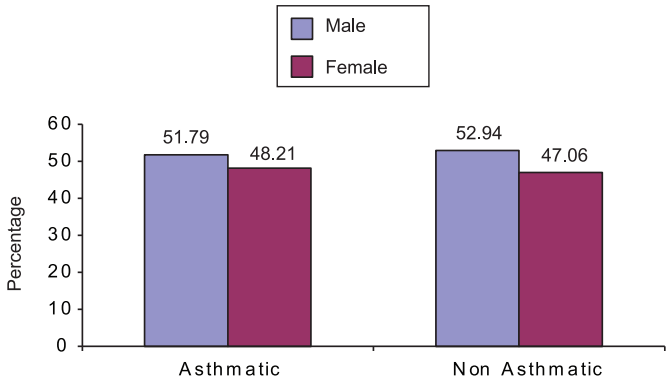


Fig.-2: *Sex distribution of the study patients.*

Table-III

Distribution of the study patients according to actual FEV_1 in liter (n=107)

FEV_1	Asthmatic (n=56) Mean ±SD	Non Asthmatic (n=51) Mean ±SD	Pvalue
Mannitol (mg) (n=108)			
Baseline	2.79±0.77	2.92±0.82	0.370^{ns}
Range (Min-Max)	(1.49-4.22)	(1.67-4.35)	
After test	2.42±0.74	2.78±0.77	0.015^{s}
Range (Min-Max)	(1.24-4.0)	(1.55-4.02)	
^{a}P value	0.001^{s}	0.001^{s}	
At recovery	2.87±1.07	2.91±0.82	0.866^{ns}
Range (min-max)	(1.46-4.16)	(1.65-4.3)	
Hypertonic saline (n=107)			
Baseline	2.8±0.8	2.9±0.8	0.397^{ns}
Range (Min-Max)	(1.5-4.1)	(1.8-4.3)	
After test	2.4±0.7	2.8±0.8	0.034^{s}
Range (Min-Max)	(1.3-3.9)	(1.2-3.9)	
^{a}P value	0.001^{s}	0.001^{s}	
At recovery	2.7±0.8	2.9±0.8	0.231^{s}
Range (min-max)	(1.5-4)	(1.7-4.3)	
Methacholine (Mg/Ml) (n=75)			
Baseline	2.75±0.78	3.02±0.77	0.135^{ns}
Range (Min-Max)	(1.52-4.44)	(1.76-4.16)	
After test	2.21±0.71	2.74±0.71	0.003^{s}
Range (Min-Max)	(1.22-3.82)	(1.62-3.92)	
^{a}P value	0.001^{s}	0.001^{s}	
At recovery	2.69±0.78	2.98±0.77	0.113^{ns}
Range (min-max)	(1.5-4.4)	(1.74-4.1)	

NS= Not significant, s = significant
P value reached from unpaired-t test. ^{a}P value reached from paired-t test

Table III, shows the actual FEV_1 of the study patients during baseline, after test and at recovery.

Out of 107 study patients the mean actual FEV_1 during mannitol challenge at baseline was 2.79±0.77 L, range from 1.49 to 4.22 L in asthmatic patients and 2.92±0.82 L, range from 1.67 to 4.35 L in non-asthmatic patients. The mean actual FEV_1 during mannitol challenge after test was 2.42±0.74 L, range from 1.24 to 4.0 L in asthmatic patients and 2.78±0.77 L, and range from 1.55 to 4.02 L in non-asthmatic patients. Mean actual FEV_1 difference within the groups between baseline and after test was significant ($p<0.05$) in paired t-test in both groups. And the mean actual FEV_1 during mannitol challenge at recovery was observed 2.87±1.07 L, range from 1.46 to 4.16 L in asthmatic patients and 2.91±0.82 L, range from 1.65 to 4.3 L in non-asthmatic patients.

Out of 107 study patients the mean actual FEV_1 during hypertonic saline challenge at baseline was observed 2.8±0.8 L, range from 1.5 to 4.1 L in asthmatic patients and 2.9±0.8 L, range from 1.8 to 4.3 L in non-asthmatic patients. The mean actual FEV_1 during hypertonic saline challenge after test was 2.4±0.7 L, range from 1.3 to 3.9 L in asthmatic patients and 2.8±0.8 L, and range from 1.2 to 3.9 L in non-asthmatic patients. Mean actual FEV_1 difference within the groups between baseline and after test was significant ($p<0.05$) in paired t-test in both groups. And the mean actual FEV_1 during hypertonic saline challenge at recovery was observed 2.7±0.8 L, range from 1.5 to 4.0 L in

asthmatic patients and 2.9±0.8 L, range from 1.7 to 4.3 L in non-asthmatic patients.

Out of 75 study patients the mean actual FEV_1 during methacholine challenge at baseline was observed 2.75±0.78 L, range from 1.52 to 4.4 L in asthmatic patients and 3.02±0.77 L, range from 1.76 to 4.16 L in non-asthmatic patients. The mean actual FEV_1 during methacholine challenge after test was observed 2.21±0.71 L, range from 1.22 to 3.82 L in asthmatic patients and 2.74±0.71 L, range from 1.62 to 3.92 L in non-asthmatic patients. Mean actual FEV_1 difference within the groups between baseline and after test was significant ($p<0.05$) in paired t-test in both groups. And the mean actual FEV_1 during methacholine challenge at recovery was observed 2.69±0.78 L, range from 1.5 to 4.4 L in asthmatic patients and 2.98±0.77 L, range from 1.74 to 4.1 L in non-asthmatic patients. FEV_1 during baseline and at recovery were not statistically significant ($p>0.05$) but after test Mannitol, Hypertonic saline and Methacholine were statistically significant ($p<0.05$) between two groups.

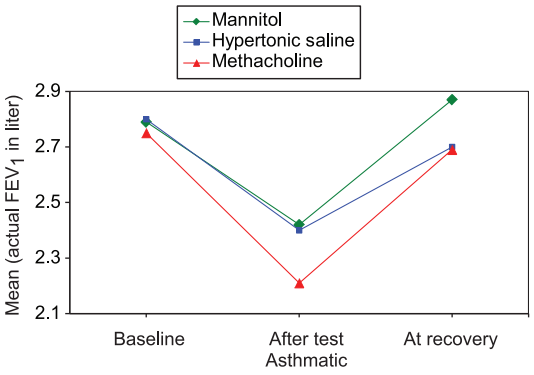


Fig.-3: *Line diagram showing the mean actual FEV_1 of the asthmatic patients during baseline, after test and at recovery.*

Figure 3 shows the actual FEV_1 of the asthmatic patients during baseline, after test and at recovery. At baseline actual FEV_1 was almost similar in three groups, however after test all three groups decline significantly but more mark in methacholine group, however, at recovery all three groups towards baseline.

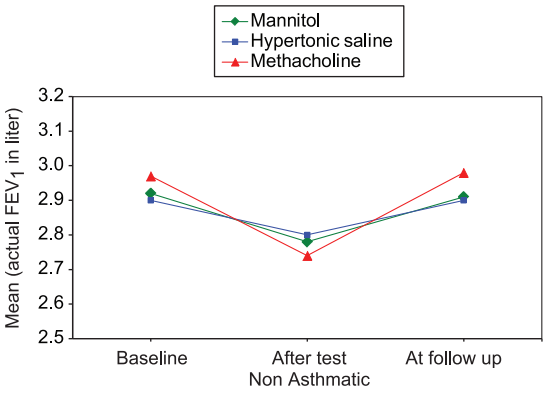


Fig.-4: *Line diagram showing the mean actual FEV_1 of the non-asthmatic group during baseline, after test and at recovery.*

Figure 4 shows the actual FEV_1 of the non asthmatic group during baseline, after test and at recovery. At baseline actual FEV_1 was almost similar in three groups, however after test all three groups decline significantly but more mark in methacholine group, however, at recovery all three groups towards baseline.

Table-IV

Distribution of the study patients according to provocating concentration in positive cases of different provocating substances in different intervention (n=107)

Mannitol (mg)	Asthmatic (n=56)		Non Asthmatic (n=51)	
	n	%	n	%
75	8	20.0	0	0
155	14	35.0	0	0
315	7	17.5	1	100
475	9	22.5	0	0
635	2	5.0	0	0
Total	40	100	1	100
Hypertonic saline (%)				
4.5	17	40.5	0	0
9.0	11	26.2	1	50.0
13.5	14	33.3	1	50.0
Total	42	100	2	100
Methacholine (Mg/Ml)				
0.025	1	2.4	1	12.5
0.25	8	19.5	0	0.0
2.50	10	24.4	2	25.0
10.0	22	53.7	5	62.5
Total	41	100	8	100.0

Table IV shows the provocating concentration of different provocating substances of the study patients in different interventions. In case of Mannitol bronchoprovocation test, out of 41 positive patients, maximum 14 patients had positive at 155 mg of cumulative doses of mannitol concentration in patients with asthmatic. However, 42 positive patients in Hypertonic saline group, most 18 patients had positive at 4.5% hypertonic saline concentration in patients with asthmatic.. In case of Methacholine bronchoprovocation test, out of 50 positive patients, 27 patients positive at 2.50 mg/ml methacholine concentration in patients with asthmatic. Patients with non-asthmatic Methacholine bronchoprovocation test, was found maximum positive and 5 subjects positive at 10.0 mg/ml methacholine concentration.

Table-V

Comparison among Mannitol, Hypertonic saline and Methacholine bronchoprovocation test.

Test of validity	Mannitol	Hypertonic saline	Methacholine
Sensitivity	71.0	75.0	98.0
Specificity	98.0	96.0	76.0
Accuracy	84.11	85.04	88.0
Positive predictive value	97.6	95.5	83.67
Negative predictive value	75.8	77.8	96.15

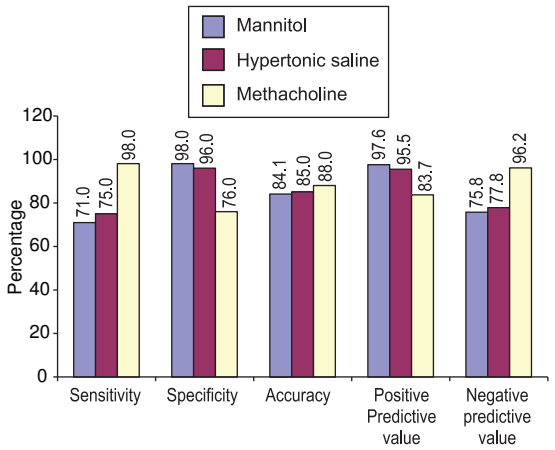


Fig.-5: *Comparison among Mannitol, Hypertonic saline and Methacholine bronchoprovocation test*

Table-VI

Adverse events during various bronchoprovocation test. (n=107)

Adverse events	Asthmatic (n=56)		Non Asthmatic (n=51)		P value
	n	%	n	%	
Mannitol:					
No complaints	34	60.7	41	80.4	0.026[s]
Had complaints	22	39.3	10	19.6	
Cough		11	50.00	06	60.00
Wheeze	06	27.27	00	00.00	
Nausea	02	09.10	03	30.00	
Other complaints		03	13.63	01	10.00
Hypertonic saline:					
No complaints	26	64.3	37	72.5	0.359[ns]
Had complaints	30	357.	14	27.5	
Cough	12	40.00	06	42.86	
Wheeze	9	30.00	00	00.00	
Nausea	4	13.33	07	50.50	
Other complaints	05	16.67	01	07.14	
	Asthmatic (n=42)		Non Asthmatic (n=33)		
	n	%	n	%	
Methacholine:					
No complaints	27	64.3	36	78.8	0.170[ns]
Had complaints	29	35.7	15	21.2	
Cough		10	34.48	10	66.68
Wheeze	12	41.38	03	20.00	
Nausea	05	17.24	01	06.66	
Other complaints		02	06.90	01	06.66

S=Significant, NS=Not significant, P value reached from chi square test.

Table VI shows the adverse events during Mannitol provocation test and observed that, 34(60.7%) in asthmatic patients and 41(80.4%) in non-asthmatic had no complains. Cough was found 11(50.0%) and 2(3.9%) in Asthmatic and non Asthmatic group respectively. Wheeze 6(27.27%) in Asthmatic and not found in non Asthmatic group. Nausea 2(9.10%) in Asthmatic and 3(30.0%) in non Asthmatic group. Others complain 3(13.6%) in Asthmatic and 1(10.0%) in non Asthmatic group. Statistically significant ($p<0.05$) difference was observed in Chi square test.

The adverse events during Hypertonic saline provocation test and observed that, 26(64.3%) in asthmatic patients and 37(72.5%) in non-asthmatic had no complains. Cough was found 12(40.0%) and 6(42.86%) in Asthmatic and non Asthmatic group respectively. Wheeze 9(30.0%) in Asthmatic and 0(0.0%) in non Asthmatic group. Nausea 4(13.3%) in Asthmatic and 7(50.50%) in non Asthmatic group. Others complain 5(16.67%) in Asthmatic and

1(7.14%) in non Asthmatic group. Statistically not significant (p>0.05) difference was observed in Chi square test.

The adverse events during Methacholine provocation test and observed that, 27(64.3%) in asthmatic patients and 36(78.8%) in non-asthmatic had no complains. Cough was found 10(34.48%) and 10(66.67%) in Asthmatic and non Asthmatic group respectively. Wheeze 12(41.38%) in Asthmatic and 3(20.0%) in non Asthmatic group. Nausea 5(17.24%) in Asthmatic and 1(6.66%) in non Asthmatic group. Others complain 2(6.90% in Asthmatic and 1(6.66%) in non Asthmatic group. Statistically not significant (p>0.05) difference was observed in Chi square test.

Cough and wheeze were more common in Methacholine and Hypertonic saline and commonest complain was in Asthmatic patients.

Discussion:

This double blind, randomized, crossover study was carried out with an aim to find out the efficacy and safety of inhaled dry powder mannitol as bronchoprovocation test for airway hyper responsiveness and also to compare the efficacy and safety of inhaled dry powder mannitol with hypertonic saline and methacholine as bronchoprovocation test for airway hyper responsiveness.

A total of 107 subjects ranging from 15 to 50 years were finally included in the study. Asthmatic subjects those had active signs and symptoms of mild to moderate asthma according to the Expert panel report 2 criteria considered as case and unrelated healthy volunteers with no respiratory symptoms was recruited as control subjects in the National Institute of Disease of the Chest and Hospital (NIDCH), Mohakhali, Dhaka. During February 2010- January 2011.

In this current study among the 107 subjects , out of which 56 asthmatic patient's age range from 15 to 50 years and 51 non-asthmatic subjects age range from 18 to 50 years. The mean±SD age was 34.52±10.37 years and 34.15±9.45 years in asthmatic patients and non-asthmatic subjects respectively. The mean age was almost similar between two groups. Anderson et al. studied the airway sensitivity to inhaled mannitol, the repeatability of the response, and the recovery after challenge in 43 asthmatic subjects with 18 to 39 years of age[11]. On the other hand, Brannan et al. recruited higher age range in their study, which was 6 to 83 years subject with Asthmatics and non-asthmatics[12].

In this present study it was observed that male was predominant in both group, which was 51.79% and 52.94% in asthmatic and non-asthmatic subjects respectively and male female ratio was 1.1:1 in the whole study. No significant (p>0.05) difference was observed regarding the sex distribution between two groups. A similar study by Anderson et al. has shown male female ratio was almost 1: 3.[11] Another study conducted by Brannan et al. found male 47.0% and 46.0% in safety and efficacy population.[12] The mean height and weight were almost (p>0.05) similar between two groups.

Mean pulse rate, SBP, DBP, respiratory rate and SpO_2 (Oxygen saturation) were almost similar, at baseline, after test and at recovery between two groups, but significantly decline after test within group from baseline in both groups. Almost similar findings obtained by Brannan et al. and Anderson et al. regarding the mean pulse rate, SBP, DBP, respiratory rate and SpO_2 (Oxygen saturation).[11,12]

In this study it was observed that the mean actual FEV_1 during mannitol challenge at baseline was 2.79±0.77 L, with range from 1.49 to 4.22 L in asthmatic patients and 2.92±0.82 L, with range from 1.67 to 4.35 L in non-asthmatic patients. The mean actual FEV_1 during mannitol challenge after test was decline both groups, which was 2.42±0.74 L, with range from 1.24 to 4.0 L in asthmatic patients and 2.78±0.77 L, with range from 1.55 to 4.02 L in non-asthmatic patients. The mean actual FEV_1 during mannitol challenge at recovery was increased both groups, which was 2.87±1.07 L; with range from 1.46 to 4.16 L in asthmatic patients and 2.91±0.82 L, with ranged from 1.65 to 4.3 L in non-asthmatic patients. FEV_1 after test Mannitol, was statistically significant (p<0.05) between two groups but during baseline and at recovery were not statistically significant (p>0.05).

The mean actual FEV_1 during hypertonic saline challenge at baseline was observed 2.8±0.8 L, with range from 1.5 to 4.1 L in asthmatic patients and 2.9±0.8 L, with range from 1.8 to 4.3 L in non-asthmatic patients. The mean actual FEV_1 during hypertonic saline challenge after test was decline

groups, which were 2.4±0.7 L, range from 1.3 to 3.9 L in asthmatic patients and 2.8±0.8 L, range from 1.2 to 3.9 L in non-asthmatic patients. And the mean actual FEV_1 during hypertonic saline challenge at recovery was almost similar with at baseline, which was 2.7±0.8 L, with range from 1.5 to 4.0 L in asthmatic patients and 2.9±0.8 L, with range from 1.7 to 4.3 L in non-asthmatic patients. FEV_1 after test Hypertonic saline was statistically significant ($p<0.05$) between two groups but during baseline and at recovery were not statistically significant ($p>0.05$).

The mean actual FEV_1 during methacholine challenge at baseline was observed 2.75±0.78 L, with range from 1.52 to 4.4 L in asthmatic patients and 3.02±0.77 L, with range from 1.76 to 4.16 L in non-asthmatic patients. The mean actual FEV_1 during methacholine challenge after test was decline both groups, which was 2.21±0.71 L, with range from 1.22 to 3.82 L in asthmatic patients and 2.74±0.71 L, with range from 1.62 to 3.92 L in non-asthmatic patients. And the mean actual FEV_1 during methacholine challenge at recovery was almost similar at baseline, which was 2.69±0.78 L, with range from 1.5 to 4.4 L in asthmatic patients and 2.98±0.77 L, with range from 1.74 to 4.1 L in non-asthmatic patients. FEV_1 after test Methacholine was statistically significant ($p<0.05$) between two groups but during baseline and at recovery were not statistically significant ($p>0.05$).

In this current study it was found that the provocating concentration of different provocating substances of the study patients in different interventions. In case of Mannitol bronchoprovocation test, out of 41 positive patients, maximum 14 patients had positive at 155 mg of mannitol concentration in patients with asthmatic. However, 42 positive patients in hypertonic saline group, most 18 patients had positive at 4.5% hypertonic saline concentration in patients with asthmatic. In case of Methacholine bronchoprovocation test, out of 50 positive patients, 27 patients positive at 2.50 mg/ml methacholine concentration in patients with asthmatic. Patients with non-asthmatic Methacholine broncho-provocation test, was found maximum positive and 5 subjects positive at 10.0 mg/ml methacholine concentration.

In this current study out of 107 cases, 41(38.32%) were positive and 66(61.68) were negative in mannitol bronchoprovocation test. Among 56 asthmatic patients 40 (71.4%) cases observed positive and 16 (28.6%) cases observed negative in mannitol challenge test. However, among 51 non-asthmatic patients only 1(1.96%) observed positive and all other cases 50(98.04%) observed negative in mannitol bronchoprovocation test. Sensitivity was found 71%, Specificity 98%, Accuracy 84.1%, Positive predictive value 97.6%, Negative predictive value 75.8%, Likelihood ratio for a positive test result 36, Likelihood ratio for a negative test result 0.29, Pretest probability (prevalence in the study) 52.3, Post test probability for positive test 98 and Post test probability for negative test 24. Anderson et al.found similar result in their study.[11]

In this present hypertonic saline broncho-provocation test out of 107 cases, 44 were positive and 63 were negative in. Among 56 asthmatic patients 42(75.0%) observed positive and 14(25.0%) observed negative in hypertonic saline bronchoprovocation test. However, among 51 non-asthmatic patients, only 2(3.92%) cases observed positive and all other cases 49(96.08) observed negative in hypertonic saline bronchoprovocation test. Sensitivity was found 75%, Specificity 96%, Accuracy 85.04%, Positive predictive value 95.5%, Negative predictive value 77.8%, Likelihood ratio for a positive test result 19, Likelihood ratio for a negative test result 0.26, Pretest probability (prevalence in the study) 52.3, Post test probability for positive test 95 and Post test probability for negative test 22. Brannan *et al*. obtained almost similar Sensitivity and specificity in their study.[12]

In this present Methacholine bronchoprovocation test out of 75 cases, 49(65.33%) were positive and 26(34.67%) were negative in Among 42 asthmatic patients 41(97.62%) observed positive and 01(2.38%) observed negative in Methacholine bronchoprovocation test. However, among 33 non-asthmatic patients 08(24.24%) observed positive and 25(75.76%) observed negative in Methacholine bronchoprovocation test. Sensitivity was 98.0%, Specificity 76.0%, Accuracy 88.3%, Positive predictive value 83.7%, Negative predictive value 96.2%, Likelihood ratio for a positive test result 4.03, Likelihood ratio for a negative test result

0.03, Pretest probability (prevalence in the study) 56.6, Post test probability for positive test 84 and Post test probability for negative test 4. . Anderson et al. also found similar result in their study.[11]

In this current study it was observed that Methacholine bronchoprovocation test was highly sensitive (98.0%) but less Specific, however Mannitol and Hypertonic bronchoprovocation test was highly Specific (98.0%) in Mannitol and 96.0% in Hypertonic saline) but less sensitive (71.0% Mannitol and 75.0% in Hypertonic saline).

In this present series out of 41 cases, true positive cases of methacholine bronchoprovocation test, only 31(75.60%) cases observed positive and 10(24.40%) cases observed negative in mannitol bronchoprovocation test. Among the 25 true negative cases of methacholine bronchoprovocation test, all are observed negative in mannitol provocation test. Sensitivity was 76%, Specificity 100.0%, Accuracy 84.84%, Positive predictive value 100.0%, Negative predictive value 71.42%, Likelihood ratio for a positive test result (Inf.), Likelihood ratio for a negative test result 0.24, Pretest probability (prevalence in the study) 62.61, Post test probability for positive test 100.

In this present series out of 41 true positive and 25 true negative cases of methacholine bronchoprovocation test, only 33 were observed positive and all others negative in hypertonic saline bronchoprovocation test. Sensitivity was 80%, Specificity 100%, Accuracy 87.87%, Positive predictive value 100%, Negative predictive value 75.75%, Likelihood ratio for a positive test result (Inf.), Likelihood ratio for a negative test result 0.20, Pretest probability (prevalence in the study) 62.1 and Post test probability 100.

In this present study, 42 true positive and 49 true negative cases of hypertonic saline bronchoprovocation test, only 39 were observed positive and all others negative in mannitol bronchoprovocation test. Sensitivity was 93.0%, Specificity 100.0%, Accuracy 96.70%, Positive predictive value 100.0%, Negative predictive value 94.23%, Likelihood ratio for a positive test result (Inf.), Likelihood ratio for a negative test result 0.07, Pretest probability (prevalence in the study) 46.2, Post test probability for positive test 100.0 and Post test probability for negative test 6.

Brannan et al. have shown sensitivity of mannitol to identify hypertonic saline positive was 80.7% and the specificity 86.7%. [12] The sensitivity of mannitol compared with the clinical assessment was 59.8% and specificity 95.2%. The sensitivity and specificity of the present study is higher than the above author's findings, which may due to small number of sample size in the current study. The mannitol BPT provides a standardized and rapid point-of-need test to identify currently active asthma.[13]

Regarding the adverse events during Mannitol provocation test in this study it was observed that, 34(60.7%) in asthmatic patients and 41(80.4%) in non-asthmatic had no complains. Cough was found 11(50.0%) and 6(60.0%) in Asthmatic and non Asthmatic group respectively. Wheeze 6(27.7%) in Asthmatic and 0(0.0%) in non Asthmatic group. Nausea 2(9.10%) in Asthmatic and 3(30.0%) in non Asthmatic group. Others complain 3(13.6%) in Asthmatic and 1(10.0%) in non Asthmatic group.

The adverse events during Hypertonic saline provocation test and observed that, 26(64.3%) in asthmatic patients and 37(72.5%) in non-asthmatic had no complains. Cough was found 12(40.04%) and 6(42.86%) in Asthmatic and non Asthmatic group respectively. Wheeze 9(30.0%) in Asthmatic and 0(0.0%) in non Asthmatic group. Nausea 4(13.3%) in Asthmatic and 7(50.5%) in non Asthmatic group. Others complain 5(16.67% in Asthmatic and 1(7.14%) in non Asthmatic group.

The adverse events during Methacholine provocation test and observed that, 27(64.3%) in asthmatic patients and 36(78.8%) in non-asthmatic had no complains. Cough was found 10(34.4%) and 10(66.6%) in Asthmatic and non Asthmatic group respectively. Wheeze 12(41.3%) in Asthmatic and 3(20.0%) in non Asthmatic group. Nausea 5(17.2%) in Asthmatic and 1(6.6%) in non Asthmatic group. Others complain 82(6.9%) in Asthmatic and 1(6.6%) in non Asthmatic group. Cough and Wheeze are more common during Mannitol provocation, hypertonic saline provocation test and Methacholine provocation test in Asthmatic patients. In brief, cough was more common in Mannitol and Methacholine than Hypertonic saline in and wheeze was second commonest complain in Asthmatic patients. Brannan et al. mentioned that adverse events were monitored and diaries

kept for 7 days following the tests. The diarised events were similar for mannitol and HS, the most common being nausea (4.3%M, 3%HS), and cough (2.2%M, 2.4%HS). [12]

In the future, mannitol BCT may be added to lung function and symptom assessment to aid in the everyday management of asthma.[13]Mannitol challenge is an accepted testing method in Australia, Europe, and Korea. Acceptance of the mannitol challenge in the United States would complement existing methods for assessing bronchial hyperreactivity and likely improve patient care.[14] A positive response to indirect stimuli is suggestive of active inflammation and AHR that is consistent with a diagnosis of asthma. Persons with a positive response to indirect stimuli benefit from daily treatment with inhaled corticosteroids.[15]

Limitations of the Study:

There were some limitations in this study like; Population sample studied is not representative of whole Bangladesh. Age limit (10 to 50 years) for inclusion criteria may be extended in both ends. All patients were not enrolled in all three challenges.

Conclusion:

This double blind, randomized, crossover study was carried out to find out the efficacy and safety of inhaled dry powder mannitol as bronchoprovocation test for airway hyper responsiveness and compare its safety and efficacy with hypertonic saline and methacholine. In this study it was found that; the mannitol BPT was found safe and well tolerated. No serious adverse events were recorded.

Based on an analysis of patients with a clinical diagnosis of asthma, mannitol PD15 had sensitivity

of 71.0% to detect the presence of asthma and specificity of 98.0% for clinical diagnosis of asthma.

Mannitol PD15 had a sensitivity of 93.0% and specificity of 100.0% with respect to PD15 for

hypertonic saline. Mannitol PD15 had a sensitivity of 76.0% and specificity of 100.0% with respect to

PC20 for Methacholine.

Although the sensitivity, specificity, Accuracy, Positive predictive value and Negative predictive value are almost similar between Hypertonic saline and mannitol but mannitol bronchoprovocation test is easier to perform, tasteless as well as convenient and patient friendly, so mannitol bronchoprovocation test is now preferred. In the future, mannitol BCT may be added to lung function and symptom assessment to aid in the everyday management of asthma.[13]

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ORIGINAL ARTICLE

Gene Xpert MTB/RIF Test for Rapid Diagnosis of Tuberculous Lymphadenitis from Fine Needle Aspirate

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Abstract:

Routinely Tuberculous lymphadenitis (TBLN) is diagnosed by fine-needle-aspiration cytology (FNAC) or histopathology. During treatment many cases may be relapsed, failed or converted to cold abscess. Gene Xpert MTB/RIF is a new diagnostic tool for bacteriologic evidence of Tuberculous lymphadenitis. Xpert MTB/RIF can detect TBLN rapidly (within 2 hr) and play role in the categorization of TB treatment. This study was done at NTRL, NIDCH, Mohakhali, and Dhaka, Bangladesh from February, 2013 to October, 2013.

Adequate (>0.5ml) amount of fine-needle aspirate (FNA)/biopsy materials were collected from both new & previously treated suspected TBLN cases. These specimens were processed for AFB- C/S in MGIT system, DST were done and sediment from the specimens were used for Xpert MTB/RIF. FNA/biopsy material was also analyzed by cytology or histopathology for tissue diagnosis. All the suspected TBLN cases were followed up for at least 2 months after starting anti-TB drugs. Repeat sample was done for patients with inadequate response to anti-TB drugs to exclude other diagnosis. Finally, the results were analyzed at SPSS-20 version and the obtained results of Xpert MTB/RIF were compared to CRS.

Thirty (30) cases were selected, among them 15 (50%) were new cases and 15 (50%) were re-treatment cases. There were 10 (33.3%) male and 20 (66.7%) female. 28 (93.3%) cases were TBLN and 2 (6.7%) were other cases; one of them was Sarcoidosis and the other one was Non Hodgkin Lymphoma. All the patients were in between 15-54 year age group. Xpert MTB/RIF detected 23 (76.7%) cases and 7 (23.3%) cases were undetected. There were 4 cases of MDR-TBLN, of which

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2 were Culture proven. With comparison to CRS, the sensitivity and specificity of the Xpert MTB/RIF tests were 82.14% (95% CI- 63.09 to 93.87), 100% (95% CI- 19.29% to 100%) respectively; the sensitivity and specificity of AFB-C/S were 32.14% (95% CI- 15.91% to 52.35%), 100% (95% CI- 19.29% to 100%) respectively.

Xpert MTB/ RIF can detect TBLN rapidly with high sensitivity and specificity.

Key Ward: *Tuberculous Lymphadenitis, Gene Xpert MTB/RIF.*

[Chest & Heart Journal 2014; 38(2) : 80-85]

Introduction:

Tuberculous lymphadenitis is the most common extra-pulmonary manifestation of tuberculosis (TB), [1 2] and the majority of cases have no active lung involvement. Tuberculosis is a disease of great antiquity. Tuberculous lesion has been found in the vertebrate of Neolithic man in Europe & in Egyptian mummies dating possibly from as early as 3700BC.

Today TB has been the most important communicable disease in the world.[3] In 2012, WHO, estimated that there were 8.6million incidence of TB and 1.3 million people died from the disease.

Bangladesh ranked sixth on the list of 22 highest TB burden countries in the world. The WHO estimated that in 2010 there were approximately 411 TB cases (all form) per thousand populations. It is estimated that per 100000 people 225 new cases occur each year. Of these, approximately 100 per 100000 was infectious (smear positive). It is further, estimated that about 51 per 100000 people die of tuberculosis each year. Drug resistance, among the new cases was 2.5% (now in 2012, MDR-TB in new case 1.4%,95% CI .7-2.5, retreatment cases 29%, 95% CI 24-34 in Bangladesh and among re-treatment case was 15%. Annual risk of infection was 2.14. The HIV prevalence in adult was about less than 0.1% .The global annual incidence estimate is 9.4 million cases, of which 1.98 million cases are from India.

TB remains the largest infectious killer disease affecting adults in developing countries. [4] In India, TB disproportionately involves the young. [5] More than 90% of global TB cases and deaths occur in developing world , where 75% of cases are in the most economically productive age group (15-54 years (TB Guideline, 2010).

According to Revised National Tuberculosis Control Programmes, 0.8 million new cases of extra-pulmonary TB (EPTB) were observed in 2010. Less than 5% of new and previously treated TB patients were tested for MDR-TB in most countries in 2010. In India and China, almost 50% of multidrug-resistant TB (MDR-TB) cases worldwide are estimated to occur. In India, 15 to 20% of TB cases are estimated to be cases of EPTB, which affects mainly the lymph nodes, meninges, kidney, spine, and growing ends of the bones. [6] Since the causative agent Mycobacterium tuberculosis spreads from person to person, an efficient as well as rapid diagnosis is a key objective of worldwide tuberculosis control programmes.

Materials and Methods:

Place of study: This method comparison study was carried out in the indoor and outdoor of National Institute of Diseases of the Chest and Hospital (NIDCH), & NTRL, NIDCH, Mohakhali, Dhaka. As NIDCH is the only referral centre in Bangladesh and patients are coming from every corner of the country, the patients selected from NIDCH represent to some extent the whole Bangladesh.

This study has been carried out from February 2013 to October 2013.

Study Population: The population sample was patients aged 15-54 yrs of either sex clinically & histopathologically/cytologically proved both New and Re-treatment Tuberculous Lymphadenitis TBNA.

I had taken 30 patients having the selection criteria of TBLN.

All the samples were collected purposively on the background of cytological/ histopathological &/ clinically suspicion of TBLN patients. Adequate (>0.5ml) amount of fine-needle aspirate(FNA) materials were collected from both new & previously treated suspected TBNA cases .These specimens were processed for AFB- C/S in MGIT system and DST were done. The remaining

sediments were used for Gene Xpert MTB/RIF test. Another FNA material/ excised material were processed for FNAC/Histopathology.

All tissues were homogenized by tissue homoginator before decontamination. Sufficient (.5ml-2ml) amount of all samples were decontaminated by mixing properly with equal volume of 4% NaOH(NALc-NaOH). After 15 minutes, phosphate buffer saline (PBS) solution (pH 6.8) was added to make the final volume 45 ml. The sample was centrifuged at 3000g for 15 minutes, and the pellet was subjected to further analysis. Supernatant was discarded and vortex the sediment. Inoculate .5ml at plane MGIT and +ve tube was done for DST/AST procedure. Xpert MTB/RIF-from the remaining sediment; it mixed with reagent(SR) at 1:3 ratio, kept 15 minutes and took 2ml into the Xpert Cartridge, then inserted the cartridge at Xpert machine: the final interpreted result came out.

Informed written consent was taken from all the patients after full explanation of the nature, purpose & potential risk of all procedures which would be used for the study.

Criteria of selection of patients:

Inclusion criteria:

1. Adult population (15-54yr) irrespective of sex.
2. Patient compatible with Tuberculous lymphadenopathy and /clinical manifestation.
3. Patient who agreed to undergo necessary investigations and to give written consent.

Exclusion criteria:

1. Patient who did not agree to undergo necessary investigations and to give written consent.
2. Patients did not compatible with Tuberculous lymphadenopathy

A standard questionnaire was designed with view to collect data. Laboratory findings were collected. The questionnaire was prepared in English and expressed to the patients in local language.

The accumulated questionnaire was analyzed to find out patients who met the cytological/ histopthological and/ the clinical inclusion criteria. These patients were selected for step-3.

Medical history and clinical feature was properly evaluated. Baseline assessment including complete blood count, Chest X-ray, measurement of height and weight was done. Collection of sputum for AFB, Pus/Tissue for Xpert MTB/RIF & AFB-C/S & DST and other necessary tests were done. All the patients were followed up at least for 2 months after starting anti-TB.

A standard proforma and questionnaire was filled up for each patient. All the selected patients provided CAT-1, CAT-2 & MDR-TB drugs according to WHO recommendation.

Data were recorded systematically in a preformed data collection sheet and were analyzed.

All the collected data were analyzed statistically by SPSS (Statistical Package for Social Science)-20 version in order to arrive at definitive conclusion in respect of comparison to CRS with Xpert MTB/RIF.

Result:

30 cases were selected as per inclusion criteria. Twenty (66.67%) patients were female and 10 (33.3%) patients were male (Table 1). Out of them 4 (13.3%) patients were below 20 years and 4 (13.3%) patients above 35 years and the remaining 22 (73.3%) patients were in between 20 to 35 years of age group (Table 1). Among all the cases 15 (50%) were new cases without any treatment and 15 (50%) were old who were receiving treatment (Table 1).

Table-I

Demographic characteristics and status of TB treatment of patients

		Number	Frequency
AGE	<20 years	4	13.3%
	20-35 years	22	73.3%
	>35 years	4	13.3%
SEX	Male	10	33.3%
	Female	20	66.67%
Status of TB treatment	New	15	50%
	Old	15	50%

Twenty-eight (93.3%) patients has TBLN as per clinical and cytomorphological feature who has responded to anti-TB confirmed after a 2 months of follow-up. One (3.3%) patient had Non-Hodgkins lymphoma and one had Sarcoidosis (3.3%) (Table-2)

Table-II

Results of Xpert, AFB culture, FNAC and Histopathology among TB patient

	Positive			Negative		
	New	Old	Total	New	Old	Total
Xpert-MTB/RIF	12	11	23 (76.7%)	3	4	7 (23.3%)
AFB culture	7	2	9 (30%)	8	13	21 (70%)
FNAC or Histopathology	15	13	28 (93.33%)	0	2	2 (6.66%)

Xpert MTB/RIF detected total 23(76.7%) cases, and were negative for total 7(23.3%) cases. Among them 12 were new &11 were old. AFB-C/S detected total 9(30%) cases and does not detect 21 (70%) cases; among them 7 cases were new & 2 cases were re-treatment cases (Table-2).

Composite Reference standard- cytology/ histopathology of TBLN, outcome after follow up of 2 months treatment of Anti-TB Drugs & AFB-C/S.

Compared to the composite reference standard, Xpert MTB/RIF correctly identified 23 out of 28 TB cases (sensitivity, 82.14%; 95% CI, 63.09 to 93.87) (Table 3). Inadequate sample or blood contamination may be a cause of possible false-negative result among 5 patients. Xpert MTB/RIF was negative in two cases, with negative cytomorphology and culture (specificity, 100%; 95% CI, 19.29 to 100) (Table 3). No false positive result for Xpert MTB/RIF test was found in new cases. The Xpert MTB/RIF test was positive in all 9 smear-negative culture-positive cases among them 7 were new cases and 2 were old cases. Xpert MTB/RIF test detected 4 rifampicin resistant cases and out of them 2 cases were found MDR-TB by AFB culture and sensitivity (1 new and 1 old case).

Table-III

Comparison of Xpert and AFB culture with composite reference standard

Composite		Reference standard			Sensitivity	Specificity	PPV	NPV	LR+Ve	LR-Ve
		Features of TB	Others	Total	82.14% 95% CI (63 to 94)	100% 95% CI (19 to 100)	100% 95% CI (85 to 100%)	28.57% 95% CI (5 to 71%)	“	0.18 95% CI (0 to 0.4)
Xpert-MTB/RIF	Positive	23	0	23						
	Negative	5	2	7						
	Totals	28	2	30						
AFB culture in new case	Positive	7	0	7	46.67 % 95% CI (21 to 73)		39% 95% CI (20-61%)	100% 95% CI (59 to 100%)	1.5 95% CI (1 to 2%)	0
	Negative	8	0	8						
	Totals	15	0	15						
AFB culture in re-treatment case	Positive	2	0	2	15.38 % 95% CI (2 to 45 %)	100.00 % 95% CI (19 to 100%)				
	Negative	11	2	13						
	Totals	13	2	15						

Discussion:

It is very difficult to diagnose TBLN definitely. It ranges from so-called therapeutic diagnosis to open biopsy with histopathology and tissue culture. [7] The open biopsies with tissue culture are accepted as the gold standard to diagnose TBLN. Culture test has variable sensitivities of 3-80% in various clinical EPTB samples and it takes 4-8 weeks to get tubercle bacilli. [8] Culture requires bio-safety measures, and need trained laboratory personnel. The diagnosis of TBLN is challenging for a number of reasons: the lack of adequate sample amounts or volumes; the apportioning of the sample for various diagnostic tests (histopathology/cytology, biochemical analysis, microbiology, and Xpert MTB/RIF), resulting in non-uniform distribution of microorganisms; the pauci-bacillary nature of the specimens; the presence of inhibitors that undermine the performance of nucleic acid amplication-based techniques; and the lack of an efficient sample processing technique universally applicable on all types of extra pulmonary samples.

Molecular techniques have substantially changed the field of tuberculosis diagnosis and have been proven to yield rapid results while being highly sensitive. [9] Numerous PCR assays employing a number of different M. tuberculosis targets have recently described. [10] The new Xpert MTB/RIF assay tested in my study target the rifampicin resistance –associated rpoB gene region by heminested PCR with three specific primers and combines the sensitive detection of M.tuberculosis DNA and determination of Rifampicin resistance. Furthermore, the hands-on time is short due to automation of bacterial lysis, DNA extraction, real-time PCR amplification, and amplicon detection in a single system. A recent study showed the high sensitivity and specificity over 97% of the Xpert assay for pulmonary specimens. [9] Numerous studies have assayed the yield of PCR techniques for the diagnosis of extra-pulmonary tuberculosis.[11-13] Nevertheless, this is the first study in Bangladesh to verify the usefulness of application of Xpert MTB/RIF assay for the rapid diagnosis of TBLN. Overall, the sensitivity and specificity of the Xpert MTB/RIF were 82.14% (95% CI-63.09-93.87) and 100% (95% CI-19.29-100) in comparison to CRS.

Of the 30 recruited patients, cytomorphological features associated with TBLN were seen in 28 (93.3%) patients, Non-Hodgkins lymphoma in 1 (3.3%) and sarcoidosis (3.3%) in 1 patient (Table 1). Compared to the composite reference standard, Xpert MTB/RIF correctly identified 23(82.14%) out of 28 TBLN cases (Table-2). Inadequate sample or blood contamination may be a cause of possible false-negative result among 5 patients. Xpert MTB/RIF was negative in 2 cases with negative cytomorphology and culture (specificity, 100%). No false positive result for Xpert MTB/RIF test was found in new cases. Therefore Xpert MTB/RIF test is very specific for newly diagnosed TBLN cases. The Xpert MTB/RIF test was positive in all 9 smear-negative culture-positive cases among them 7 were new cases and 2 were re-treatment cases. Xpert MTB/RIF test/assay detected 4 rifampicin resistance cases and out of them, 2 cases were found MDR-TBLN by culture and sensitivity (1 new and 1 re-treatment case). In my study, the AFB-C/S on MGIT System revealed that it was 32.14% sensitive & 100% specific in all cases with comparision to CRS. The low sensitivity of C/S (53%) in tissue demonstated by Vadwai et al.2011 in comparision with that of the Xpert test (81%) against the CRS can be explained as follows: (A) Xpert positive re-treatment cases previously received Anti-TB drugs; (B) The paucibacillary nature of extrapulmonary specimens with a tendency of M.Tuberculosis to form clumps leads to an uneven distributionof the bacilli; (C) There is loss of viable bacilli during NALC-NaOH processing.

All the 28 TBLN patients were provided Anti-TB drugs according WHO-TB Guideline and followed for up to 2 months. Further evaluation revealed that among the 5 Xpert MTB/RIF negative cases, one was non-specific lymphadenitis, 2 cases were paradoxical immune reaction, 2 cases were not specified; in these cases steroid may give a good result and further follow up will be needed. NO NTM-TBLN cases were identified in the study. Adequate sample collection from lymph node depends on the staging of the node, biopsy needs for stage-1 and 2 and FNA for stage-3 and above.

The average time to results for microbiological culture was 14 days (range, 12 to 30 days); while the Xpert MTB/RIF test result was available within 2 h of commencing the test. This represents a substantial reduction in diagnostic delay, thereby

permitting real-time decision making and planning of treatment. [14] Study limitations include the fact that the research was conducted among new cases and among the patient who has already received cat-1 treatment and HIV is not endemic in the study area.

Conclusion:

Xpert MTB/RIF test is a simple procedure which can be performed in an outpatient setting by clinicians or nursing staff after a short training period.[15,16] It is ideal for use in resource-limited settings, including more remote and rural areas. [16] Specimen collection is simple and safe. With the use of a transport vial, virtually no sample preparation is required and there is minimal risk of contamination. Furthermore, the transmission risk to the operator may also be reduced. Combining FNA and rapid genotypic diagnosis using automated systems should greatly improve access to appropriate diagnosis and treatment for patients with tuberculous lymphadenitis.

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ORIGINAL ARTICLE

Inhaler Technique, Education and Frequency of Outdoor Visit by Asthma Patients

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Abstract:

Introduction: *Asthma is a common condition that affects around 10% of the population. It is a considerable health care problem in Bangladesh. A key issue in proper management of asthma is use of inhaler in appropriate technique which needs patient education. Poor inhaler technique may lead to increased morbidity with frequent hospital visit.*

Methods: *It was a cross sectional study conducted at Dhaka Medical College Hospital outdoor. Patient must have a documented diagnosis of asthma. Patients of the study visited the outdoor between July 2014 and December 2014. Use of inhaler pattern and their frequency of outdoor visit was observed and analyzed.*

Result: *Approximately two third of the Forty enrolled patient did not receive any formal education about asthma. Inhaler technique of 82% patient was faulty. Those who use spacer, two third used it in incorrect way. Outdoor visit is higher among the patients who used the devices in wrong way.*

Conclusion: *This study shows that incorrect use of inhaler is common in patient visiting hospital outdoor. Picture is likely to be similar in other health care facilities too. More focus should be given in the asthma education including inhaler techniques in asthma management plan.*

Key words: Asthma, Asthma education, Inhaler technique.

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Introduction:

Asthma in Bangladesh seems to be considerable health care problem with the prevalence of 6.9%.[1] Being a chronic medical condition a key issue in real management of asthma is proper education about it including use of inhalers in correct way. It is increasingly being documented that poor inhaler and/or spacer technique act as a backlog in achieving asthma control that leads to increasing morbidity and hospital visits.

The ultimate goal of patient education in asthma is to reduce the impact of asthma on related morbidity and quality of life.[2] Asthma control can be achieved by avoidance of trigger, patients adherence to preventer medications and use of

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inhalers through proper technique. All of these need patient education about asthma. The purpose of asthma education is therefore to help the patient to develop knowledge and skill to control asthma attacks and hospital stay.

Asthma education is an essential component of asthma disease management.[3] All healthcare providers at every point of care should emphasis on education including proper use of devices. It improves asthma outcome and decreases hospital visit. A patient who repeatedly visits the hospital or other healthcare site correction of his inhaler technique might be the best initial strategy to decrease morbidity and mortality.

Methods:

This was a cross sectional study conducted at Respiratory Medicine outdoor of Dhaka Medical College Hospital (DMCH). Forty patients with diagnosis of bronchial asthma were enrolled who visited the outdoor between July 2014 and December 2014. The enrolled patient must have a clinically and spirometrically documented diagnosis of asthma.

During the visit we collected information regarding demographic data, the duration of illness, the medications used for asthma, whether the patient received any formal asthma education or not. They were asked to show method they practice to use inhalers. Number of visits they made in the study period was also recorded. All the data were verified checking their medical documents.

The collected data were analyzed using SPSS (version 16). Descriptive statistics such as mean, standard deviation or median were used to summarize age and duration of asthma. Percentage were used to summarize pattern of inhalers and spacer use. The mean difference of hospital outdoor visit number between the correct and incorrect inhaler users was compared by independent sample t-test.

Results:

Forty (n=40) asthma patient were enrolled in this study. Of the 40 patient, 52.5% were male and 47.5% were female. The patient demographics are shown in table 1.

Table-I

Patient demographics

Variable		Mean±SD	Frequency	Percentage
Age		43.7±14.4		
Sex				
	Male		21	52.5
	Female		19	47.5

Table-II

Frequency of inhaler use

		Frequency	Percent	Valid Percent	Cumulative Percent
Inhaler Use	Yes	18	45.0	45.0	45.0
	No	22	55.0	55.0	100.0
	Total	40	100.0	100.0	

Table-ll shows 45% (n=18) of the patients used inhalers and 55%(n=22) did not. No missing case was in the data related to inhaler use. Among the patients who use inhaler only 22% (n=4) used it in correct way. Rest of the 78% (n=18) patient's inhaler use pattern was faulty as shown in figure-1.

The figure ll shows the spacer use pattern among the inhaler users where 72% (n=13) of the patients had never used spacer, 17% (n=3) used it in a faulty way, the procedure was correct only in 11% (n=2).

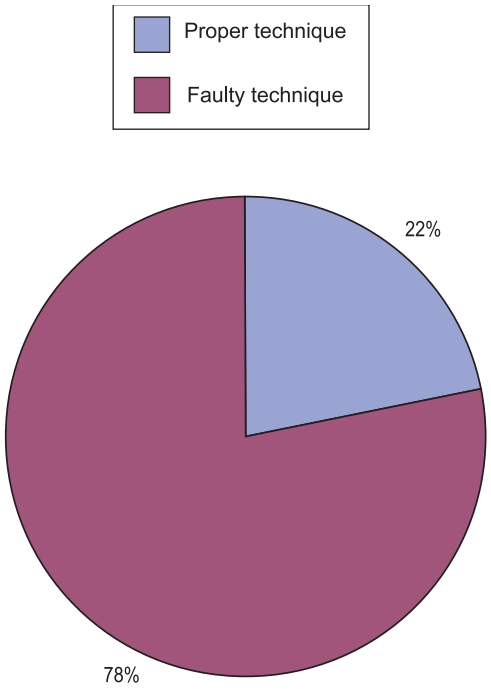

Fig.-1: Inhaler technique

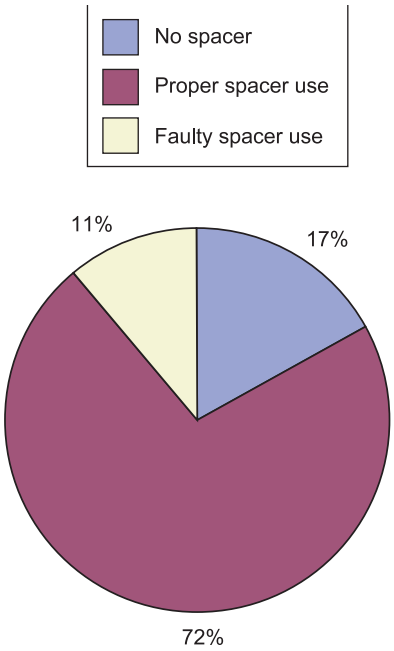

Fig.-2: Spacer use pattern

In table- lll cross tabulation between inhaler education and number of hospital visit shows that providing inhaler education for the patient decreases OPD visit substantially. Three or more visit is 5% (n=2) over the study period in patients who got inhaler education, Frequency is much higher (32.5%) who did not get it.

Number of hospital visits are significantly higher among the patient who did not receive inhaler education assuming 95% confidence interval (p< 0.05) as shown in table-lV

Table-III

Inhaler education and OPD visit frequency

		Number of OPD visit				Total
		>3		<3		
Inhaler education	Yes	2	5%	14	35%	16
	No	13	32.5%	11	27.5%	24
Total	15	5	37.5%	25	62.5%	40

**Cross tabulation

Table-lV

Comparison of mean OPD visit

Inhaler education		N	Mean	Std. Deviation	P value
Hospital visit	Yes	16	1.2500	.57735	<.05
	No	24	2.0417	.85867	

** Independent sample t-test was done to measure the level of significance.

Discussion:

While this study is not epidemiological no study on the effect of inhaler education yet taken place in the largest medical college of Bangladesh. The major strength of this study lies in the direct interviewing the patients and confirmation of the information obtained by medical records. It is very vital to examine these factors because the study observed that many patients depend on repeated outdoor visit for asthma management. Knowing this factor may help address some of the deficiencies in our attitude and focus toward the asthma patients. The national and international guidelines for the management of bronchial asthma emphasize patient education to have priority lack of which is the first line pitfall of asthma management.

This study shows that a good number of patients do not get proper inhaler technique education though vast majority are on inhaler treatment. Often drugs are changed or switched without giving emphasis on proper inhaler technique.[3,4] Thus most of the patients repeatedly visits doctor despite having optimum number of medications including inhalers with or without spacers.

The result of the study raises concern regarding current asthma management system which requires far better concentration on asthma education including inhaler technique. In this study 78% of the patient takes inhaler in a faulty way. This is primarily due to the lack of responsibility & commitment of the health care providers and lack of trained asthma educator in the asthma management system. Over burden of the patients in OPD hinders adequate time in inhaler education, on the other hand due to wrong technique of inhaler use patients repeatedly visit hospital. This is a vicious cycle.

Devices significantly contribute to asthma control.[5-7] It is clear that this study has identified a major problem in our health care problem. Similar to other studies abroad the lack of asthma education is the major reason for the repeated OPD visit in Bangladesh too.[8]

The study is based only on a single teaching hospital and may not reflect the situation at national level. The population parameter at country level may in fact be worse one. However, this study reflects the general characteristics and pitfalls of asthma management.

Conclusion:

Lack of asthma education leads to use of inhalers in faulty way which is ultimately a major cause of asthma treatment failure that leads to frequent hospital visit. National asthma studies are necessary to explore this problem and to prospectively study the value of an interventional asthma education program to improve asthma inhaler device use and clinical treatment outcomes.

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ORIGINAL ARTICLE

Platelet Count : An Indicator of Systemic Inflammation in COPD Patients.

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Abstract:

Chronic Obstructive Pulmonary Disease (COPD) is the major cause of chronic morbidity and mortality throughout the world. GOLD estimates suggest that COPD will rise from the sixth to the third most common causes of death worldwide by 2020[1]. It is a chronic disease of pulmonary system having many systemic and extrapulmonary effects in addition to pulmonary problems like cough, sputum, dyspnoea. With the passage of time, the severity of disease also increases and complications like pneumothorax , respiratory failure, pulmonary hypertension , cor-pulmonale, polycythemia , hyperviscosity syndrome, anorexia, weight loss occur due to pulmonary as well as systemic inflammation from which complete recovery is not possible. Measurement of inflammatory maker is difficult but platelet counts are less costly, easy and available in many health center. The present study was conducted to see if platelet count may be accepted as an indicator of systemic inflammation. This study was done to find out the platelet counts as a systemic inflammatory marker in COPD patients and to compare the platelet counts between COPD patients & normal persons. It was carried out in Department of Medicine (indoor & outdoor), Rajshahi Medical College Hospital from January ,2010 to December,2011. 67 (Sixty seven) spirometrically diagnosed COPD patients and 69 apparently healthy people were included. All of that study sample were free from taking any antiplatelet drugs and free from any preexisting diseases which causes platelet count alteration. This exclusion was done by history, through clinical examination and relevant investigations. Maximum platelet count of COPD was 670 x 10^3 / µL and minimum was 174 x 10^3 / µL. Patients with COPD had increased circulating platelet count (10^3 / µL) compared with controls (mean ± SD) 325.54± 87.32 vs 204.32 ± 60.56, with a p *value d" 0.001. Platelet count also was increased in relation to severity of COPD but which was not statistically significant.*

So Platelet count can be considered as marker of inflammation in COPD patients.

Key words: COPD, Polatelet count, Systemic inflammation.

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Inroduction :

Chronic Obstructive Pulmonary Disease (COPD) is also a disease of increasing public health importance around the world. GOLD estimates suggest that COPD will rise from the sixth to the third most common causes of death worldwide by 2020.[1,19] COPD is the fourth leading causes of death and affects > 16 million persons in the United States.

COPD is a preventable and treatable pulmonary disease with some significant extra–pulmonary

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effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by air flow limitation that is not fully reversible but usually progressive and is associated with an abnormal inflammatory response of the lung tissue to noxious particle or gases.[1]

This definition, however, emphasizes the importance of inflammatory processes present in COPD. This provides a mechanistic link among multiple organs leading to the complex interacting systemic manifestations that account for most of the considered morbidity and mortality in COPD patients.[2,3,19]

Inflammation is believed to play a central role in the pathogenesis of COPD. Many studies showed that inflammatory cells namely neutrophils , macrophages, lymphocytes infiltrating the airway walls.[3,5,7-13.]

COPD is often associated with clinical manifestations that include metabolic abnormalities, weight loss , muscle weakness and wasting , cardiovascular disease (e.g. atherothrombosis, ischaemic heart disease , stroke and coronary death), depression , osteoporosis, cancer and anaemia.[13]

There is a rapidly growing body of evidence indicating that the pulmonary disease observed in patients with COPD is also associated with systemic inflammation.[7] Gan et al.2004, reviewed 14 original studies that reported on the relationship between COPD , FEV1 (or forced vital capacity) and levels of various systemic inflammatory markers , namely C- reactive protein (CRP), fibrinogen , leukocytes, tumour necrosis factor (TNF) -á and IL-6 and -8. This analysis indicated that reduced lung function was significantly correlated with elevated levels of systemic inflammatory markers.[7]

Many of the systemic co morbidities associated with COPD have been related to systemic inflammation. The relationship between COPD , systemic inflammation and cardiovascular disease is of particular importance , since more than one-half of all patients with COPD die from cardiovascular causes.[9,12.]

Sin and Man analyzed data from 6,629 participants in the Third National Health and Nutrition Examination Survey to determine whether CRP and other systemic inflammatory markers were present in those with chronic airflow obstruction and whether or not they were associated with cardiac disease.[14] Individuals with severe airflow obstruction had circulating neutrophil, platelet, fibrinogen and CRP levels that were markedly higher than those in participants without airflow obstruction and the relationships between lung function and the systemic inflammatory markers were statistically significant.[14,15]

Materals and Methods:

67(sixty seven) recently spirometrically diagnosed COPD patients and 69 (sixty nine) apparently healthy people were included. This study was carried out in Department of Medicine (Indoor & outdoor) of Rajshahi Medical College Hospital from January/2010 to December/2011.Both male & female were included with age of the study population were from 30 years to 70 years. All of that study sample were free from taking any antiplatelet drugs and free from any preexisting diseases which causes platelet count alteration. This exclusion was done by history, through clinical examination and relevant investigations. After providing informed consent, the patients underwent a physical examination and chest radiographies were provided. Blood samples were obtained for ESR, CRP, leukocyte and platelet counts. Platelet counts were done by automatic analyzer in Rajshahi medical college model no. Celltac E-Nihon KohdenHoriba ABx penta 80. Spirometry was performed by Desktop spirometer (Spirolab *III* MIR 980067REV1.9). The data were analyzed with the help of SPSS software program version-16.0 descriptive analytical techniques involving frequency distribution computation of percentage, mean SD etc was applied. Association between variables was conducted applying chi-square and T- test. P-value <0.05 was considered as significant.

Results:

A total 136 persons were included in this study, 67 [male =65(97.02%), female=2(2.98%) were COPD patient considered as case group rest 69 [male=66 (95.65%), female=3(4.35%) apparently normal healthy people (without COPD) were considered as control group. Mean age of case & control group were 56.88 ± 10.20 and 52.35± 10.45.

Platelet count (10^3/μL) of the COPD & healthy person were 325.54 ±87.33 & 204.32±60.57. ESR (mm in 1st hr) of the COPD & healthy person were 9.38± 3.86 and 6.43 ± 1.56.CRP (IU/L) of the COPD & healthy person were 9.04 ±4.35 and 6.00±00. Total WBC count (10^3/μL) of the COPD & healthy person were 9.85 ±3.56 and8.15±2.80. Neutrophil count (10^3/μL) of the COPD & healthy person were 6.55±3.19 & 5.60 ±2.51. FEV^1/FVC (%) of the COPD & healthy person were 60.01±11.99 and 98.41±12.90.All the parameters between COPD and normal person were statistically significant.

Platelet counting ((10^3/μL± SD)) among COPD patients were stage-1 (275.80 ± 18.36), stage-2 (301.50 ± 36.17), stage-3 (324.44 ± 69.14) and stage-4 (339.97 ± 96.16) with a *p* value 0.276 which was not statistically significant.

Table-I

Investigation findings of subjects with and without COPD (Mean ± SD)

	COPD	Without COPD	*p- value*
Age	56.88±10.20	52.35±10.45	*0.012*
Platelet count(10^3/μL)	325.54 ±87.33	204.32±60.57	<0.001
ESR(mm in 1st hr)	9.38 ± 3.87	6.43 ± 1.57	0.001
CRP (IU/L)	9.04 ± 4.35	6.00 ±0.00	<0.001
Total WBC count(10^3/μL)	9.85 ± 3.56	8.15 ± 2.80	0.002
Neutrophil count(10^3/μL)	6.55 ± 3.19	5.60 ± 2.51	<0.001
FEV1/FVC (%)	60.01± 11.99	98.41± 12.90	<0.001

Table-II

The characteristics of COPD patients according to the stage of the disease.

	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**	*P*- value
Platelet count(10^3/μL)	275.80 ±18.36	301.50 ±36.17	324.44 ± 69.14	339.97 ± 96.16	0.276
ESR(mm in 1st hr)	9.60 ± 6.54	6.90 ± 3.63	7.50 ± 3.43	6.92 ± 3.50	0.502
CRP	7.20 ± 2.68	8.40 ± 3.10	10.13 ±4.76	11.67 ± 5.73	0.129
Total WBC count(10^3/μL)	7.38 ± 1.75	9.84 ± 2.48	9.40 ± 3.90	10.40 ± 3.77	0.325
Neutrophil count(10^3/μL)	5.10 ± 1.26	7.18 ± 2.10	6.72 ± 3.72	8.33 ± 3.17	0.093
FVC	3.45 ± .44	2.68 ±0 .61	1.98 ± .72	1.25 ± .25	
FVC%	92.00 ±6.16	81.01 ± 5.83	67.31 ± 11.36	38.42 ± 9.80	<0.001
FEV1	2.31 ± 0.21	1.66 ± 0.39	1.04 ± .34	0.56 ± .13	<0.001
FEV1%	83.60 ± 3.36	60.100± 9.31	45.06 ± 8.38	20.39 ± 5.04	<0.001
FEV1/FVC	63.70 ± 8.71	58.12 ± 3.75	52.93 ± 6.94	51.34 ± 4.38	0.069

Discussion:

Gulfidan et al showed in their study in Turkey in 2009, average age (yrs) of case group is 49.70 and control group 59.82 , Platelet count (10^3/μL) of case group is 279.303 ± 67.540 and control group 260.210± 74.162 with a *p* value < 0.047, FEV1/FVC (%) of case group is 55.93±9.54 and control group is 80.26 ± 41.10 with p <0.001. They also showed that platelet count increase in relation to severity of COPD which was statistically significant.

In our study platelet count (10^3/μL) of the COPD & healthy person were 325.537 and 204.319 respectively and standard deviation were ± 87.32 & ± 60.56 respectively with p<0.001 which consistent with the above study. Platelet count also increase in relation to severity of COPD but statistically not significant.

Arschang et al showed in their study in Austria in 2008, platelet count (10^3/μL) in COPD exacerbation was 279, in stable COPD was 273 and control was 268 with significant p value which also consistent with my study.

Another study carried out by Maclay et al in Edinburg University of UK, in 2010, showed that platelet count (10^3/μL) in COPD exacerbation was 333, in stable COPD was 290 with p = 0.09 and in COPD was 262 in comparison to control was 196 with p=0.001 which also consistent with my study.

Conclusion:

Platelet count significantly increased in COPD patients in our country compare with healthy person and also increase in relation to severity.

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ORIGINAL ARTICLE

Chemical Pleurodesis for Malignant Pleural Effusion- A Comparative Study between Bleomycin and Tetracycline Hydrochloride

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Abstract:

Objectives: *To compare the efficacy of tetracycline and bleomycin for chemical pleurodesis in the management of malignant pleural effusion.*

Method: *This prospective clinical study was conducted in NIDCH during the period one year. According to inclusion criteria sixty (60) patients of malignant pleural effusion were selected for whom pleurodesis was performed. They were divided into two groups. One group received inj. Tetracycline for pleurodesis, and the other group received inj. Bleomycin. A number variables were recorded including post pleurodesis complications, follow up and recurrence. All patients were followed up at 15 days and at 30 days after the procedure. Data were recorded and analysed accordingly.*

Result: *This study shows that there is no statistically significant difference in post pleurodesis complaints of dyspnoea and x-ray findings during 1st and 2nd follow up between the groups (p>0.05). As for the outcome of pleurodesis by groups, in the tetracycline group 6 (20.0%) patients developed recurrence within 15 days and 15 (62.5%) patients developed recurrence within 30 days of pleurodesis. In the bleomycin group 8 (26.7%) patients developed recurrence within 15 days and 17 (77.3%) patients developed recurrence within 30 days of pleurodesis. There is no statistically significant difference in development of recurrence within 15 days and recurrence within 30 days of pleurodesis between the groups (p>0.05).*

Conclusion: *It can be concluded from our study that the use of tetracycline for pleurodesis in malignant pleural effusion is as effective and safe as bleomycin in terms of recurrence and complications.*

Key words: *Pleurodesis, Chemical bleomycin, Tetracycline in pleurodesis, Malignant pleural effection.*

[Chest & Heart Journal 2014; 38(2): 95-103]

Introduction:

Pleurodesis is a procedure to produce adhesions between visceral and parietal pleurae obliterating the potential pleural space.[1] Pleurodesis is carried out to prevent re accumulation of the effusion, relief of symptoms and avoid the need for repeated

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hospitalization for thoracocentesis.[2,3] Over the past 70 years many agents have been given intrapleurally in an attempt to create a pleurodesis.[4] In general the selection of a sclerosing agent is made easier by practical considerations of avaliability, cost, effectiveness, comfort of the patient and incidence of side effects.[5] The agents used have included radioisotopes, quinacrine, antineoplastics (nitrogen mustard, bleomycin, mitoxantrone), tetracycline derivatives (tetracycline, doxycycline, minocycline), talc, erythromycin, sodium hydroxide, silver nitrate, iodopovidone, killed *Corynebacterium parvum* and OK-432 which is an immunostimulant obtained from *Streptococcus pyogenes*.[4]

Pleural effusions containing malignant cells are called malignant pleural effusion.[6] The accumulation of pleural fluid in patients with cancer signals advanced disease.[7]

Although nearly all types of malignancies can be the causes of malignant pleural effusions, most commonly by carcinomas of the breast, lung, gastrointestinal tract or ovary and by lymphomas.[1,8]

Tube thoracostomy with chemical pleurodesis using doxycycline or bleomycin is the mainstay of current treatment and is about 85.0% effective.[9]

Commonly used chemicals for pleurodesis in malignant effusions are talc and bleomycin. Tetracycline has gained acceptance in the last two decades as the pleurodesis agent of choice. It has been proven as safe, effective, inexpensive and easily administered.[10] Side effects are almost same as other agents but some times it is painful.[11] More over pleurodesis with bleomycin is costly, for which many patients in our country can not afford it. So use of tetracycline or its analogue for pleurodesis is rationally feasible for our country.

The aim of our study was to assess the comparison of efficacy of tetracycline with that of bleomycin in pleurodesis as a palliative treatment of malignant pleural effusion. The study will enrich our knowledge about the management of malignant pleural effusion among the Bangladeshi population.

Malignant pleural effusion is a major problem associated with primary and metastatic pleural malignancies, seen in approximately 50.0% of patients.[11]

The main goals of treatment for pleural effusion are to decrease symptoms and improve quality of life. The most common approaches are pleural effusion drainage and pleurodesis[11]. Chemical pleurodesis can be palliative for symptomatic malignant pleural effusions. The typical duration of hospitalization for chemical pleurodesis is 5 to 7 days. Much of this time is a consequence of prolonged chest tube drainage both prior to and immediately following pleurodesis.[7]

In many developing countries like Bangladesh, tetracycline can be used for chemical pleurodesis as it is available and safe. Side effects are almost same as other agents but some times it is painful. More over pleurodesis with bleomycin is costly, for which many patients in our country cannot afford it. Use of bleomycin for pleurodesis in malignant pleural effusion is established worldwide. The present study was conducted to compare the efficacy and side effects of tetracycline and bleomycin in patients with malignant pleural effusion. Numerous clinical studies have been performed to determine the optimal pleurodesis strategy in abroad but study among the Bangladeshi population is not yet available.

Objectives of the Study:

To compare the efficacy of tetracycline and bleomycin for chemical pleurodesis in the management of malignant pleural effusion.

a) To evaluate and compare the complications following intrapleural instillation of tetracycline and bleomycin.

b) To compare the rate of recurrence of effusion by tetracycline and bleomycin given intrapleuraly for chemical pleurodesis in the treatment of malignant pleural effusion.

Materials and Methods:

This prospective observational study was conducted in a year in the Department of Thoracic Surgery, National Institute of Diseases of the Chest and Hospital, Dhaka. A total of 60 cases of malignant pleural effusions were taken and they were divided in two equal groups having 30 patients in each group. Using random allocation procedure 30 Patients were assigned to group-A receiving tetracycline and 30 to group-B receiving bleomycin.

Sample was selected from the diagnosed case of malignant pleural effusion. Specimen from the

patient was collected by Direct Pleural biopsy, Pleurocentesis and Cytology, CT guided FNAC, Broncoscopic Biopsy & Lymphnodes Biopsy (Supraclavicular) for histopathological study.

a) Inclusion criteria:

i. Patients with diagnosed malignant pleural effusions, primary or metastatic.

ii. Should have evidence of complete expansion of underlying lung after tube thoracostomy.

iii. Patients with IT collection less than 100ml/ 24hours for 3(three) consecutive days.

b) Exclusion Criteria:

i. Patients with incomplete expansion of underlying lung.

ii. Patients with broncho-pleural fistula.

iii. Empyema

iv. History of previous chemical pleurodesis.

v. Bilateral pleural effusion

Measures of variables :

i. Age.

ii. Sex.

iii. Weight (in kg).

iv. Co-morbidities : DM, Cardiac illness, COPD

v. Types of Tumour.

vi. Side of Pleural effusion : Right/ Left

vii. Amount of pleural effusion as assessed by CXR PAV : Massive/ Moderate

viii. Post pleurodesis complaints : Fever, Pain, Dyspnoea

ix. Day of removal of IT tube after pleurodesis.

x. Hospital stay (in days).

xi. Post pleurodesis follow up.

xii. Post pleurodesis outcome (Recurrence).

Procedure of pleurodesis :

After admission, for all patients, tube thoracostomy was done under local anaesthesia. Pleurodesis was done when lung became expanded and IT tube drainage was less than 100 ml/24 hours for 3 consecutive days. Then 20 ml of 1% lignocaine was introduced through the IT tube & the tube was clamped and waited for 15 minutes for local anaesthesia to take effect.

For Tetracycline pleurodesis then we introduced injection tetracycline hydrochloride slowly and carefully at a dose of 35 mg/kg body weight. Finally 20 ml normal saline is introduced to flush the tube.

For Bleomycin pleurodesis injection Bleomycin was introduced through the chest drain tube in a similar manner at a dose of 1mg/kg body weight (not more than 60 mg) calculated for each patient & dissolved with 1ml of D/W per mg. Again 20 ml normal saline introduced for flushing of the tube.

In both cases the IT tube was clamped for 6-8 hrs and patients were advised to change his posture hourly. The tube was unclamped after 6-8 hrs and allowed drainage.

Immediate complications such as shock, chest pain, fever and respiratory distress were recorded. It tube is removed when drainage become less than 100ml/24 hrs, usually after 24 hours. After removal of IT tube check CXR was done. After removal of IT tube, patients were referred to oncologist for further chemo or radio therapy.

All patients were discharged with advised to come on follow up for two times. 1st Follow up 15 days after pleurodesis & 2nd Follow up 30 days after pleurodesis. During each follow up the patients were evaluated clinically and radiologically by i) Dyspnea & ii) X- Ray chest. And the outcome of pleurodesis was recorded by the incidences of recurrence of malignant pleural effusion as i) Recurrence within 15 days & ii) Recurrence within 30 days.

A semi-structured questionnaire was used for data collection. Informations were collected through taking clinical history and clinical examination from patients under going chemical pleurodesis in the department of Surgery of NIDCH, Dhaka. A written informed consent was taken from the patients.

Statistical analysis of the results was obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-15) (SPSS Inc, Chicago, IL, USA). The results were presented in tables and diagrams.

Prior to commencement of this study, the research protocol was approved by ethical committee of National Institute of Diseases of the Chest & Hospital.

Results:

Among the 60 patients who received pleurodesis 35 were males and 25 females. Most of the patients fell into the 40-60 years age group (47/60). Mean ± SD of age of the tetracycline group and bleomycin group were 53.23 ± 8.50 years and 50.57 ± 10.34 years respectively. Among the co-morbidities, 16 patients had Diabetes, 4 had cardiac illnesses and 19 were suffering from COPD having almost equal distribution among the two groups.

Out of 30 patients in tetracycline group two third (66.7) had secondary tumour and one third (33.3%) had primary tumour. Out of 30 patients in bleomycin group 19 (63.3%) had secondary tumour and 11 (36.7%) had primary tumour. Secondaries came from the breast, ovaries different parts of GIT and others which were equally distributed among the two groups.

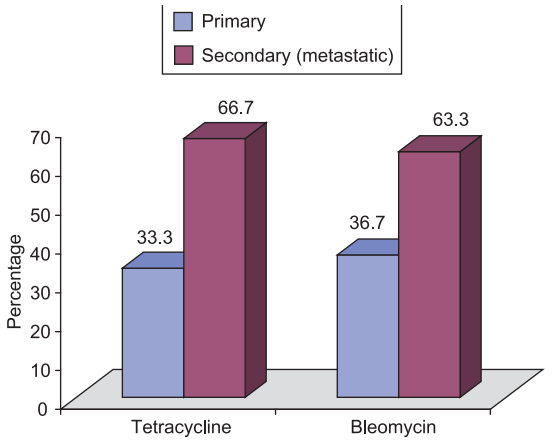

Fig.-1: *Bar diagram of type of tumour by groups*

Out of 30 patients in the tetracycline group 17 (56.7%) were in right side and 13 (43.3%) were in left side . Out of 30 patients in the bleomycin group 18 (60.0%) were in right side and 12 (40.0%) were in left side . Right and left side ratio in tetracycline group was 1:0.76 and in bleomycin group that was 1:0.67.

Table-I

Distribution of Side of malignant pleural effusion

Side of malignant pleural effusion	Groups		p value*
	Tetracycline	Bleomycin	
Right side	17 (56.7)	18 (60.0)	0.793
Left side	13 (43.3)	12 (40.0)	
Total	30 (100.0)	30 (100.0)	

*Chi-square test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Out of 30 patients in the tetracycline group, 25(83.3%) were massive (effusion crossing the anterior part of upper border of 2nd rib in CXR) and 5 (16.7%) were moderate (effusion below the 2nd rib) pleural effusion. Out of 30 patients in the bleomycin group 24 (80.0%) were massive and 6 (20.0%) were moderate pleural effusion. There is no statistically significant difference in X-ray findings before tube-thoracostomy between the groups (p>0.05).

Table-II

Amount of Pleural effusion as assessed by CXR PAV

Amount of Pleural effusion as assessed by CXR PAV	Groups		p value*
	Tetracycline	Bleomycin	
Massive (effusion crossing the anterior part of upper border of 2nd rib in)	25(83.3)	24 (80.0)	0.684
Moderate (effusion below the 2nd rib)	5 (16.7)	6 (20.0)	
Total	30 (100.0)	30 (100.0)	

*Chi-square test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Figure 2 shows the distribution of post pleurodesis complaints by both the groups. In tetracycline group the post pleurodesis complaints of fever, pain and dyspnoea were present in 23.3%, 26.7% and 3.3% respectively. In bleomycin group post pleurodesis complaints of fever and pain were present in 30.0% and 23.3% respectively. In the

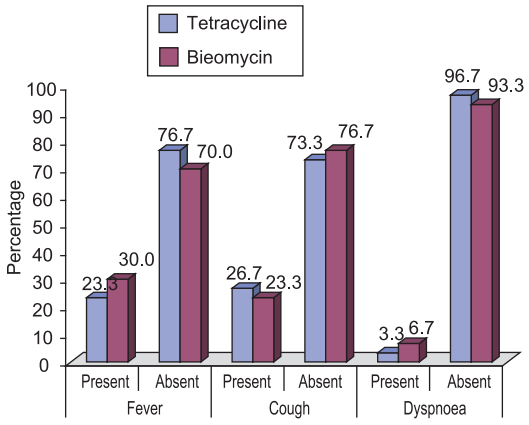

Fig.-2: *Bar diagram of post pleurodesis complaints by group*

bleomycin group 2 (6.7%) patients were presented with post pleurodesis dyspnoea. There is no statistically significant difference in post pleurodesis complaints of fever, pain and dyspnoea between the groups (p>0.05).

Table 3 shows the distribution of removal of IT tube on day by groups. In two third patients of tetracycline group IT tubes were removed on the 2nd day after the procedure and in rest one third patients IT tubes were removed on the 3rd day. In more than two third patients (70.0%) of bleomycin group IT tubes were removed on the 2nd day and in rest 9 (30.0%) patients IT tubes were removed on the 3rd day. There is no statistically significant difference in the period of time of IT tube removal between the groups (p>0.05). In all patients of both the groups the amount of fluid collection before the removal of IT tube were less than 100 ml in 24 hours.

Table-III

Distribution of IT tube removal on day after pleurodesis by groups

IT tube removed on	Groups		p value*
	Tetracycline	Bleomycin	
2nd day	20 (66.7)	21 (70.0)	0.781
3rd day	10 (33.3)	09 (30.0)	
Total	30 (100.0)	30 (100.0)	

*Chi-square test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Table 4 shows the distribution of hospital stay (in days) by groups. Mean ± SD of hospital stay of tetracycline group and bleomycin group were 11.87±1.925 days and 12.93±1.856 respectively. There is statistically significant difference in hospital stay between the groups (p<0.05).

Table-IV

Distribution of hospital stay (in days) by groups

Hospital stay (in days)	Groups		p value*
	Tetracycline	Bleomycin	
Mean ± SD	11.87±1.925	12.93±1.856	0.033

t test was done to measure the level of significance (t value =-2.185;df=58).

Table 5 shows the distribution of post pleurodesis follow up complaints of dyspnoea and x-ray findings by groups. During 1st follow up in tetracycline group 6 (20.0%) had complaints of dyspnoea and 6 (20.0%) had incomplete expansion on x-ray chest. During 2nd follow up in tetracycline group 15 (62.5%) had complaints of dyspnoea and 15 (62.5%) had incomplete expansion on x-ray chest. During 1st follow up in bleomycin group 8 (26.7%) had complaints of dyspnoea and same 8 (26.7%) had incomplete expansion on x-ray chest. During 2nd follow up in bleomycin group 17 (77.3%) had complaints of dyspnoea and same 17 (77.3%) had incomplete expansion on x-ray chest. There is no statistically significant difference in post pleurodesis complaints of dyspnoea and x-ray findings during 1st and 2nd follow up between the groups (p>0.05).

Table-V

Distribution of post pleurodesis follow up complaints of dyspnoea and x-ray findings by groups

Follow up	Groups		p value*
	Tetracycline	Bieomycin	
1st follow up (15 days after pleurodesis)			
Dyspnea			
Present	06 (20.0)	08 (26.7)	0.542
Absent	24 (80.0)	22 (73.3)	
X-ray chest			
Not fully expanded	06 (20.0)	08 (26.7)	0.542
Expanded	24 (80.0)	22 (73.3)	
2nd follow up (30 days after pleurodesis)			
Dyspnea			
Present	15 (62.5)	17 (77.3)	0.277
Absent	09 (37.5)	05 (33.7)	
X-ray chest			
Not fully expanded	15 (62.5)	17 (77.3)	0.277
Expanded	09 (37.5)	05 (33.7)	

*Chi-square test was done to measure the level of significance.

Figure within parentheses indicates in percentage.

Table 6 shows the distribution of outcome of pleurodesis by groups. In the tetracycline group 6 (20.0%) patients developed recurrence within 15 days and 15 (62.5%) patients developed recurrence within 30 days of pleurodesis. In the bleomycin group 8 (26.7%) patients developed recurrence within 15 days and 17 (77.3%) patients developed

recurrence within 30 days of pleurodesis. There is no statistically significant difference in development of recurrence within 15 days and recurrence within 30 days of pleurodesis between the groups (p>0.05).

Table-VI

Distribution of outcome of pleurodesis by groups

Outcome of pleurodesis	Groups		p value
	Tetracycline	Bieomycin	
Recurrence within 15 days			
Yes	06 (20.0)	08 (26.7)	0.542
No	24 (80.0)	22 (73.3)	
Recurrence within 30 days			
Yes	15 (62.5)	17 (77.3)	0.277
No	09 (37.5)	05 (33.7)	

*Chi-square test was done to measure the level of significance.
Figure within parentheses indicates in percentage.

Discussion:

Malignant pleural effusion is a major problem associated with primary and metastatic pleural malignancies, seen in approximately 50.0% of patients.[11,12] After the detection of pleural effusion, mean survival is only 3–12 months.[11,13] After the diagnosis of a malignant pleural effusion, the clinician must decide on the most appropriate form of palliation for the symptomatic patient.[13,14] Evacuation of the pleural fluid by means of Thoracocentesis or Tube Thoracostomy is the primary step to be taken for immediate relief of symptoms. Subsequently Pleurodesis is carried out to prevent reaccumulation of the effusion among the patients with malignant pleural effusion.[2,3] Effective pleurodesis eliminates the need for multiple hospital visits for removal of pleural fluid by thoracentesis.[15] In the symptomatic patient with a reasonable life expectancy, chemical pleurodesis appears to be the most effective and least morbid therapy.[14] Chemical pleurodesis is the most common modality of therapy for patients with recurrent, symptomatic, malignant pleural effusion.[16] Over the past 70 years many agents have been given intrapleurally in an attempt to create a pleurodesis.[4] The list of the chemical and other products that have been used to produce pleurodesis is long and ranges from antibiotics to anti- neoplastic, physical and immunological agents. In general the selection of a sclerosing agent is made easier by practical considerations of availability, cost, effectiveness, comfort of the patient and incidence of side effects.[17] Chemical pleurodesis with tetracycline has gained general acceptance as the therapy of choice.[13] Tube thoracostomy with chemical pleurodesis using doxycycline or bleomycin is the mainstay of current treatment and is about 85.0% effective.[18] Bleomycin is the most widely used antineoplastic agent for the management of malignant pleural effusion. The drawback to the use of bleomycin is the cost and the necessity for personnel familiar with the administration of cytotoxic drugs. Chest tube insertion and tetracycline pleurodesis using tetracycline capsules was found to be effective and cheap.[3] Several potentially important changes in technique have emerged since the initial description of this procedure. With adherence to meticulous technique, tetracycline pleurodesis provides rapid, effective, and safe palliation of malignant pleural effusions.[13]

The present prospective and comparative study was conducted in the Department of Thoracic Surgery, National Institute of Diseases of the Chest and Hospital, Dhaka in the span of one year. Total of 60 cases of malignant pleural effusions were taken and they were equally divided in two groups. Thirty patients were undergone pleurodesis with tetracycline and another 30 patients were undergone pleurodesis with bleomycin.

Malignant pleural effusion remains a common complication of advanced cancer.[19] Carcinoma of any organ can metastasize to the pleura, however, carcinoma of the lung is the commonest malignancy to invade the pleura and produce malignant pleural effusion.[14,20] Although nearly all types of malignancies can be the causes of malignant pleural effusions most commonly by carcinomas of the breast, lung, gastrointestinal tract or ovary and by lymphomas.[1,8] In the present study out of 30 patients in tetracycline group two third (66.7) had secondary tumour and one third (33.3%) had primary tumour. Out of 30 patients in bleomycin group 19 (63.3%) had secondary tumour and 11 (36.7%) had primary tumour. There is no statistically significant difference in type of tumour between the groups (p>0.05). Lung is primary site of tumour in highest number of patients in both tetracycline and bleomycin groups.

Other primary sites of tumour in tetracycline group were breast (26.7%), ovary (10.0%), GIT (13.3%) and others (16.7%) and in bleomycin group were breast (20.0%), ovary (6.7%), GIT (20.0%) and others (16.7%). **Laisaar et al.** in a study of ninety-eight patients of malignant pleural effusion found the most common primary cancer sites were lung (30 cases) followed by breast (25) and ovarium (11).[15] Tettey et al retrospectively studied to establish the effectiveness of tetracycline pleurodesis in malignant pleural effusion[3]. In their study out of 38 women, 32 were diagnosed as breast cancer (84%), 4 were ovarian cancer (10%), one endometrial carcinoma (3%), and one fallopian tube cancer (3%).

Typical symptoms associated with the malignant pleural effusions include dyspnea, cough and chest pain.[10,14] Dyspnea is due to a combination of reduction in ipsilateral lung volume and contralateral shift of the mediastinum. Chest pain is usually related to involvement of the parietal pleura, ribs and other intercostal structures.[10] In our study in the tetracycline group post pleurodesis complaints of fever, pain and dyspnoea were present in 23.3%, 26.7% and 3.3% respectively. In bleomycin group post pleurodesis complaints of fever and pain were present in 30.0% and 23.3% respectively and 6.7% patients in the bleomycin group were presented with post pleurodesis dyspnoea. There is no statistically significant difference in post pleurodesis complaints of pain and dyspnoea between the groups ($p>0.05$) but statistically significant difference observed in post pleurodesis complaints of fever between the groups ($p<0.05$). In a prospective, randomized trial was carried out by Martinez et al. to compare intrapleural tetracycline and bleomycin in terms of response rate and toxicity profile where they found fever was most common in bleomycin-treated patients ($p=0.024$) while pain was most frequent in the tetracycline arm (non significant).[21]

Sherman et al. in a study reviewed 108 procedures involving tube thoracostomy and tetracycline pleurodesis, reported a success rate of 94.4% without serious complications.[13] Considering all patients, 49% were symptom-free at three months. Bayly et al. reported a success rate of tetracycline pleurodesis of 67% in 12 patients with malignant pleural effusion.[22] Tag El et al. in a study reported a success rate of 60% after tetracycline pleurodesis in 12 patients with malignant pleural effusion.[23] Tettey et al. retrospectively studied to establish the effectiveness of tetracycline pleurodesis in malignant pleural effusion.[3] In their study sixty one percent of patients achieved complete symphysis of the pleura with no recurrence. There was recurrence with loculation in 16% of the cases and in 23% of patients, the procedure was unsuccessful and significant reaccumulation of pleural fluid occurred. Success rate after single administration of bleomycin varies from 58% to 85%. Martinez et al. in a prospective, randomized trial compared intrapleural tetracycline and bleomycin in terms of response rate and toxicity profile.[21] In their study the mean survival and time to relapse did not differ between the two groups. No statistically significant differences were found in terms of efficacy at each evaluation time. Overall, 16 (52.0%) and 20 (60.0%) patients had a recurrence of pleural effusion during follow-up in the tetracycline and bleomycin arms, respectively. Ruckdeschel et al. studied 115 patients at 13 centers who were entered on a randomized comparison of tetracycline and bleomycin for treatment of malignant pleural effusions.[19] In their study the median time to recurrence or progression of the effusion was 32 days for tetracycline-treated patients and at least 46 days for bleomycin-treated patients ($p = 0.037$). The recurrence rate within 30 days of instillation was 36 percent (10/28) with bleomycin and 67 percent (18/27) with tetracycline ($p = 0.023$). By 90 days the corresponding recurrence rates were 30 percent (11/37) for bleomycin and 53 percent (19/36) for tetracycline ($p = 0.047$). Walker et al. studied to provide information about available agents for chemical pleurodesis and they found that the success rates of tetracyclines and bleomycin were 67.0% and 54.0% respectively.[10] Spiegler et al. in a prospective case series study determined the feasibility of rapid pleurodesis in patients with malignant pleural effusions in order to reduce hospital length of stay in patients with a limited life expectancy.[7] In their study they found a complete response was seen in 48.0% cases, a partial response in 31.0% and 21.0% did not respond to pleurodesis.

During 1st follow up in tetracycline group 6 (20.0%) had complaints of dyspnoea and 6 (20.0%) had no

expansion of lung in x- ray chest. During 2nd follow up in tetracycline group (62.5%) patients had complaints of dyspnoea and (62.5%) had no expansion of lung in x- ray chest. During 1st follow up in bleomycin group 8 (26.7%) had complaints of dyspnoea and 8 (26.7%) had no expansion of lung in x- ray chest. During 2nd follow up in bleomycin group (77.3%) patients had complaints of dyspnoea and (77.3%) had no expansion of lung in x-ray chest. There is no statistically significant difference in post pleurodesis complaints of chest pain and dyspnoea during 1st and 2nd follow up between the groups (p>0.05). There was no serious complication associated with the procedure using tetracycline in the present study. Tettey et al. in a study observed the complications after the tetracycline pleurodesis were chest pain in 7 (18%) immediately after the introduction of the mixture into the pleural cavity and fever in 8 (21%) which lasted between 24 to 48 hours.[3]

In the tetracycline group 6 (20.0%) patients were developed recurrence within 15 days and 15 (62.5%) patients were developed recurrence within 30 days of pleurodesis. In the bleomycin group 8 (20.0%) patients were developed recurrence within 15 days and 17 (77.3%) patients were developed recurrence within 30 days of pleurodesis. There is no statistically significant difference in development of recurrence within 15 days and recurrence within 30 days of pleurodesis between the groups (p>0.05).

Conclusion:

The present study was conducted with the aim to compare the efficacy of tetracycline and bleomycin for chemical pleurodesis in the management of malignant pleural effusion. There is no statistically significant difference in development of recurrence within 30 days and recurrence within 60 days of pleurodesis between the tetracycline and bleomycin groups. There is no statistically significant difference in post pleurodesis complaints of dyspnoea, chest pain and fever between the groups. Although the study conducted with a small sample size and without long term follow up it can be concluded that use of tetracycline for the pleurodesis as effective and safe as bleomycin in terms of recurrence and complications.

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REVIEW ARTICLE

Transfusion Related Pulmonary Oedema – A Challenge

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Abstract:

Transfusion-associated circulatory overload (TACO) is cardiogenic pulmonary oedema due to infusion of rapid or large volume blood product. TACO is a frequent, serious, but under-recognized complication of haemotherapy. Presenting symptoms include dyspnoea, cyanosis, tachycardia and increased blood pressure. Pedal oedema, headache, chest tightness and dry cough are additional manifestations. Chest radiographs reveal pulmonary oedema and cardiomegaly. Vulnerable patients are the very young and persons over 60 years. While rapid infusion or massive transfusion are frequently the precipitating factors, relatively small volumes (1–2 units) are sufficient to trigger the congestive heart failure. Both haeme and non-haeme fluids account for the positive fluid balance. Fresh-frozen plasma (FFP) and autologous red blood cells have been implicated as well. Consequences include longer length of intensive care unit and hospital stay. The fatality rate has been reported to be 1–3%, but this may understate the true rate. The incidence has been reported to be 1–8% in orthopaedic surgical populations. In general hospital populations a range of 1 : 708–1 : 4075 red blood cell transfusions is associated with TACO. In the intensive care setting, an incidence of 1 : 356 components has been demonstrated. TACO is frequently confused with transfusion-related acute lung injury (TRALI). In some cases, TRALI and TACO may co-exist. A potentially important diagnostic tool is brain natriuretic peptide. Brain natriuretic peptide is elevated in TACO and a post-transfusion-to-pre-transfusion ratio of 1·5 is indicative of the diagnosis. The test has a sensitivity of 81% and a specificity of 89%. Treatment includes supplementary oxygen, diuretics, placing the patient in a sitting position and therapeutic phlebotomy in 250-ml increments. While rapid infusion is believed to be a contributing factor, optimal

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infusion rates for the non-emergency situation have not been determined. TACO has been observed with flow rates between 0·9 and 48·1 ml/min. Preventive measures include use of evidence-based transfusion and controlled-rate infusion. Measures that insure the use of standardized blood components, such as derived through apheresis, are likely to favourably impact the incidence of this complication.

If the general textbook of medicine or surgery is an indicator of the seriousness of a clinical problem, transfusion-associated circulatory overload (TACO) is a non-issue. These standard works pay little heed to this complication of haemotherapy [1]. Classic reference works of transfusion medicine are not significantly different. Mollison's Blood Transfusion in Clinical Medicine addresses TACO in one page of text [2]. The reasons for this lack of attention are due to: (i) absence of 'linkage' for transfusionists between haemotherapy and pulmonary oedema and (ii) clinical perception that circulatory causes minimal morbidity.

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Introduction:

For patients with diminished cardiac reserve, rapid infusion or large-volume infusion is most frequently the precipitating stimulus. Within 1–2 h of transfusion, the patient develops any or all of the following symptoms and signs: dyspnoea, orthopnoea, cyanosis, jugular venous distension and pedal oedema.[1-3] Tachycardia and increased systolic and diastolic blood pressure, characterized by widened pulse pressure, are frequently observed. Auscultation demonstrates the presence of rales (or worsening rales if the patient already has compromised cardiac or pulmonary status) and chest radiographs reveal an enlarged cardiac silhouette and diffuse, bilateral infiltrates. Pulmonary wedge and central venous pressure are elevated.

Incidence

In a retrospective study from a single medical centre that utilized a vigilant bedside transfusion medicine consultation service and dedicated transfusion nursing staff, Popovsky and Taswell found that 1 in 708 patients receiving red cell transfusions developed circulatory overload.[4] In this Mayo Clinic study, the mean age of those with TACO was 60 years (range 8–89). In 20% of the cases, a single unit of red blood cell was sufficient to precipitate acute respiratory distress.

Recent studies of patients undergoing knee or hip arthroplasty suggest that TACO is a frequent occurrence. In an analysis of US Medicare patients receiving perioperative blood transfusions in five hospitals, investigators found that 1% developed TACO.[3,5] The patients who developed this complication were older – 87 vs. 77 years – than those without such complications. Surprisingly, they had modest intraoperative blood loss (mean = 375 ml) and a transfusion requirement of only 1–2 units. Most importantly, these patients had a mean positive fluid balance of 2·5 l before the transfusion triggered the reaction. Patients with TACO required more intensive hospital care or treatment in the intensive care unit and longer length of hospital stay.

In a multicentre prospective study involving 9482 patients undergoing total hip or knee replacement, fluid overload necessitating the use of a diuretic was documented in 8% of patients receiving an allogeneic transfusion [range of red blood cell (RBC) units transfused = 1·8–2·7], compared with 4% receiving no red cell transfusions ($P < 0·001$) [6]. In the Quebec haemovigilance system, TACO was reported in 1 : 5561 RBC transfused, with a death rate of 1·3%.[7] For the years 2000–2004, the incidence increased from in 1 in 10 360 in 2000–2001 to 1 in 4075 in 2004.[8] This change is more likely related to increased recognition and improved reporting, rather than to a true increase.[3] Consistent with these findings is a report from the French haemovigilance system that over a 6-year period 742 cases of TACO were identified, resulting in 3·6% (27 deaths) fatality rate.[9] In aggregate, these reports indicate that TACO is frequent and clinically important.

The reports cited above refer to general patient populations. Some patient groups, however, are at increased risk. In an analysis of intensive care patients who did not require respiratory support at the time of transfusion, 25 of 49 patients (51%) with confirmed acute pulmonary oedema were

found to have TACO.[3,10] The incidence of TACO was 1 in 356 per unit transfused, compared with 1 in 534 per unit for TRALI. This incidence is 10 times higher than that has been reported in the haemovigilance reports.

Diagnosis:

Although there are clear clinical differences between TACO and TRALI, these entities are frequently confused by clinicians. At the Mayo Clinic, 80% of initial TRALI reports are subsequently diagnosed as TACO (SB Moore, personal communication, April 2006). In a recent study that used a computer-based screening programme designed to identify TRALI, a review of 88 cases of post-transfusion hypoxemia (of 820 transfusion recipients) found 10 cases of TACO – a 1·1% incidence.[11]

Recently, the clinical laboratory has provided a tool to improve the diagnosis of TACO. The cardiac marker brain natriuretic peptide (BNP) is a neurohormone that is synthesized and secreted from the ventricular myocardium in response to ventricular volume and pressure distension.[3,12] BNP was first introduced for the diagnosis of congestive heart failure. In congestive heart failure, BNP levels are elevated.

In a case–control study by Zhou *et al.*, a post-transfusion-to-pre-transfusion BNP ratio of 1·5 as a cut-off point yielded a sensitivity of 81% and a specificity of 89% for the determination of TACO.[13] In this study, only acute dyspnoea, post-transfusion systolic blood pressure elevations > 30 mmHg, and elevated BNP were statistically different between patients and controls. Tobian and colleagues found comparable sensitivity and specificity in a 30-patient study.[14] using a post-transfusion-to-pre-transfusion ratio of 1·5. Clearly, more experience will determine the usefulness of BNP in TACO, but the early results are promising.

Flow rate

Textbooks refer to 'rapid infusion' as a contributing factor for circulatory overload, but there is a paucity of data on the subject. The AABB Technical Manual recommends an infusion rate of 2–4 ml/min for red cells, and 'faster' rates for plasma and platelets.[3,15] The science behind such recommendation is sparse. Logic dictates that recipient weight should be a factor into the infusion equation. The lack of guidelines is compounded by poor control of infusion rates in many clinical settings, which is due to the inconsistent use of infusion pumps, lack of quality control of infusion pumps, and the paucity of nursing oversight of the transfusion process. To underscore this point, in one medical centre, 47 cases of TACO in adults were documented in association with infusion rates of 0·9–48·1 ml/min, with a mean of 4·5 ml/min (C Andrzejewski, personal communication; 1 November 2005).

Management:

The key elements of effective management of TACO are prompt recognition and treatment. Once TACO is suspected, the transfusion should be stopped promptly. Treatment is driven by the severity of the symptoms. The administration of supplementary oxygen, intravenous diuretics to reduce plasma volume, and placing the patient in a seated position are all treatment options.[3] When symptoms persist, repeated administration of diuretics and therapeutic phlebotomy in 250-ml increments may be indicated.

Prevention:

In susceptible patients, transfusions should be administered as slowly as the clinical situation allows. The patient should be monitored periodically during and for the first 30 min after a transfusion to detect the changes in vital signs and symptoms of overload.[3] In addition, careful attention should be paid to the patient's fluid balance (haeme and non-haeme) prior to transfusion.

The transfusion of RBC on an 'as-needed' basis would most certainly have a salutatory effect on the incidence of TACO. This necessitates the use of evidence-based decision-making for the appropriate indications. Ultimately, physicians may adopt a 'transfuse by the gram' approach for RBC. Arslan *et al.* demonstrated the value of this approach by calculating the grams of haemoglobin required for a successful patient transfusion based on the recipient's red cell mass and desired haemoglobin increment.[16] To accomplish this goal, the investigators selected units of RBC that came closest to the grams of haemoglobin required. This resulted in a 30% reduction in allogeneic RBC exposure. However, to manually select and match RBC units for every transfusion is impractical. An alternative is to standardize the component content of RBC. This is feasible through automated blood collection. Apheresis technology corrects for the differences in donor haematocrit and yields blood components that have minimal unit-to-unit differences in haemoglobin content as compared with the 30–40% variability in

manually collected units.[10,17-19] Such variability increases the likelihood of volume overload, particularly in high-risk individuals. Automated blood collection technology provides the transfusing physician with the means to more precisely meet patient transfusion needs.

Summary:
TACO is a serious complication of haemotherapy that is under-recognized. Relatively small volumes of blood components are sufficient to trigger TACO. Increased length of stay, acuity of care and increased mortality are consequences. The use of BNP may increase the frequency of diagnosis and distinguish it from TRALI. The use of evidence-based transfusion decision-making and standardized blood components should decrease the incidence of TACO.

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REVIEW ARTICLE

Genitourinary Tuberculosis , A Common Extrapulmonary Tuberculosis : it's Clinical Presentations, Diagnostic Tools and Catastrophic Complications – a Review Article

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Abstract:

The insidious onset and non-specific constitutional symptoms of genitourinary tuberculosis (GUTB) often lead to delayed diagnosis and rapid progression to a non-functioning kidney. Genitourinary tuberculosis (GUTB),is a worldwide disease, but shows a more destructive behavior in developing countries like Bangladesh. GUTB usually affects adults between the second and fourth decades of life. There is often a long latent period (5-40 years) between the original pulmonary infection and the appearance of clinical renal disease,[9] Most patients present with local symptoms such as frequent voiding; dysuria, pyuria, back or flank or abdominal pain [1-5] and microscopic or macroscopic hematuria[12] Conventionally, demonstration of mycobacterium in urine has been used as the primary test for the diagnosis of GUTB. Preferably, five consecutive early-morning specimens of urine should be examined.[21] Urine analysis of sediment from a 24-hour specimen for acid-fast bacilli (AFB) is positive in 80-90% of cases of TB. Gene X-pert test The technique of PCR is rapid, with results available within few hours of DNA extraction from the sample. It is highly specific (up to 88%) and its sensitivity in detecting urine acid-fast bacilli (AFB) has been reported in up to 94% of the cases.[22,23]A negative chest radiograph and tuberculin test cannot exclude the diagnosis of extra-pulmonary TB.[9] The intravenous urogram (IVU) remains the gold standard in imaging early renal TB. Ultrasonography is a poor modality to show morphological changes. The overall incidence of renal failure reported in the literature is 24%.[10] There are three mechanisms by which TB can cause renal failure.

Keywords: *Genitourinary Genitourinary TB, EPTB, Genital TB, Urinary TB*

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Introduction:

Tuberculosis (TB) remains a worldwide problem and its incidence appears to be increasing due to various factors, such as the spread of human immunodeficiency virus (HIV) , increase of use of immunosuppressive drugs . Tuberculosis (TB), is

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the commonest worldwide cause of mortality from infectious diseases[1] with nine million new cases and two million fatalities per year[2]. Approximately 95% of cases occur in developing countries.[1] The insidious onset and non-specific constitutional symptoms of genitourinary tuberculosis (GUTB) often lead to delayed diagnosis and rapid progression to a non-functioning kidney. Due to hematogenous dissemination of TB, there is a potential risk of involvement of the contralateral kidney too.[3] The genitourinary tract is a primary target of hematogenous infections[4] and is common site of extra-pulmonary TB,[5] comprising 14-41% of the same.[6,7] Genitourinary tuberculosis (GUTB), is a worldwide disease, but shows a more destructive behavior in developing countries. The kidney is the most common site of GUTB. The usual frequency of organ involvement is kidney, bladder, fallopian tube and scrotum.[5]

Patient Population:

GUTB usually affects adults between the second and fourth decades of life and is reported as being rare in children[8] and in the fifth and sixth decades. A mean age of 40.7 years (range: 5-90 years) has been noted.[4] There is often a long latent period (5-40 years) between the original pulmonary infection and the appearance of clinical renal disease,[9]which is probably why renal involvement is rare before the age of 20 years.The youngest reported case of urinary tract tuberculosis (UTB) was 2 years old.[10] In India, it is not uncommon to see children with UTB. They have seen TB autonephrectomy in a six year old girl.

Clinical presentations:

UTB has an insidious onset, no specific symptoms and atypical presentations,[11] which lead to difficulty and delay in diagnosis.[13-15] Most patients present with local symptoms such as frequent voiding, dysuria , pyuria, back, flank, or abdominal pain[17-19] and microscopic or macroscopic hematuria.[12] Systemic symptoms of fever, weight loss, and anorexia are less common.[17-19] The usual frequency of organ involvement is: kidney, bladder, fallopian tube, and scrotum.[5] The GUTB has varied presentation and some of the common ways are:

- Recurrent or resistant urinary tract infection, sterile pyuria with or without hematuria.[6]
- Irritative voiding symptoms, i.e., frequency, urgency, and dysuria.[6]
- An incidental diagnosis in a known case of tuberculosis.
- Renal (hydronephrosis/pyonephrosis) or epididymal mass.[6]
- Infertility and pelvic inflammatory disease.[6]
- Renal failure (Chronic kidney disease due to parenchymal infection and obstructive uropathy.[6]
- The various other ways of presentation described are: flank pain with acute pyelonephritis, non-healing wounds, sinuses, or fistulae (nephrocutaneous fistula or vesicovaginal fistula), and hemospermia.[5-9]

The most common symptoms with which the patients have presented are in the form of irritative voiding, which are found in more than 50% of the patients.

Organ specific specific clinical presentations :

Kidney and Ureter

The disease can be advanced and of long-standing nature even with very few symptoms. Many a times, the patient is asymptomatic, but may have chronic sterile pyuria. Gross hematuria is seen in only 10%, but microscopic hematuria is present in up to 50% of the cases.[11] Acute renal pain is rare. It usually occurs secondary to luminal obstruction by blood clots, sloughed renal papilla, or flakes of calcification. Chronic dull ache may be due to infundibular, pelviureteric, or ureteric stricture . Some patients present with chronic renal failure which can be either due to renal parenchymal destruction secondary to infection or due to obstructive uropathy.[9]

Urinary Bladder

Involvement of the bladder is usually secondary to renal infection and is found in nearly one-third of the patients.[12] In the early stage, i.e., acute phase, bladder changes are usually non-specific which gives rise to irritative voiding symptoms. Chronic inflammation causes reduced compliance and capacity manifesting as frequency of micturition. Urgency develops if the bladder is extensively involved. Those who develop "thimble bladder" (due to mural fibrosis and contracture) may present with urinary incontinence.[13] Chronic inflammation and extensive fibrosis at vesicoureteric junction result in "Golf-hole ureter".

Prostate, Penis and Urethra

These organs are uncommonly involved. Tuberculous prostatitis and urethritis can cause "beefy redness" and superficial ulcerations on endoscopic examination. Dilatation of the prostatic urethra, and "golf hole" dilatation of the prostatic ducts have also been reported.[15] Tuberculosis of the prostate may cause nodularity on digital rectal examination (DRE) mimicking malignancy. Sometimes, the diagnosis is made after histopathological examination of transurethral prostatectomy (TURP) chips. Very rarely, fulminating prostatic involvement can cause abscess formation and subsequent perineal fistulization.

Primary involvement of the penis may have varied presentation. It may manifest as an ulcer clinically indistinguishable from sexually transmitted diseases (STDs) or malignancy. Rarely, it can cause cavernositis and cold abscess formation presenting as penile deformity or impotence.[12] Urethral involvement leads to stricture formation causing deterioration of the urinary stream and retention. Hematospermia, although rare, may be one of the presentations of genital tuberculosis. The incidence of hematospermia has been reported in up to 11% of the cases.[17]

Epididymis and testes

Here, infection usually starts from the globus minor, as it has a richer vascularity. Usually presents as painful scrotal mass, which initially cannot be distinguished clinically from epididymo-orchitis. Sometimes, orchitis and the resulting testicular swelling can be difficult to differentiate from other mass lesions of the testes. These cases can present as infertility due to epididymal and/or vasal obstruction.[8] Nodular beading of the vas is a characteristic physical finding. Neglected cases may present as scrotal sinus.[18]

Pelvic disease in females

The association of tuberculosis and pelvic disease most frequently presents as infertility, chronic pelvic pain, alterations in the menstrual pattern, or amenorrhea.[19]

Investigations :

Urine examination

Sterile pyuria is the classic finding. Conventionally, demonstration of mycobacterium in urine has been used as the primary test for the diagnosis of GUTB. Preferably, five consecutive early-morning specimens of urine should be examined.[21] The yield of urine examination by smear and culture for detecting the tubercle bacillus is low, probably because of the intermittent shedding of the bacilli and is also observer-dependent. Direct smears are often negative (positive only in 30%) and urine cultures require 6 to 8 weeks in special culture media (Lowenstein-Jensen).[22]Sensitivity of urine culture in conventional cultural media is between 80 and 97%.[23]

Hematuria and culture-negative pyuria may be seen at urine analysis.[20] Urine analysis of sediment from a 24-hour specimen for acid-fast bacilli (AFB) is positive in 80-90% of cases of TB. Urine culture requires 6-8 weeks for diagnosis and there is a 10-20% false-negative rate.[19] Laboratory findings do not reveal the site or extent of disease, knowledge of which is imperative for further management. Imaging thus plays a major role, both in the initial workup as well as during follow-up.

Rapid Identification of Mycobacterium

Radiometric systems

Radiometric liquid culture systems (i.e., BACTEC®) [Becton Dickinson, USA]) give rapid results and are highly sensitive in the identification of mycobacterium. But these methods have some inherent difficulties in working with radioactive materials, and the necessary apparatus used are really expensive. Recently, alternative growth detection methods for liquid culture employing oxygen quenching and redox reagents have been described and commercialized, which show performance comparable to BACTEC.[23] The time needed for culture and drug sensitivity testing is about 2 to 3 weeks.

Polymerase chain reaction

Polymerase chain reaction (PCR) lets the sequence of DNA fragment from just a few mycobacteria to be amplified *in vitro* such that the amount of amplified DNA can be visualized and identified (Gene X-pert test). The technique of PCR is rapid, with results available within few hours of DNA extraction from the sample. It is highly specific (up to 88%) and its sensitivity in detecting urine acid-fast bacilli (AFB) has been reported in up to 94% of the cases.[22-23]

Imaging

A negative chest radiograph and tuberculin test cannot exclude the diagnosis of extra-pulmonary TB.[9]Only 36.5% of patients with UTB have a previous diagnosis of TB, or abnormal imaging studies[8].Evidence of active TB or an abnormal chest radiograph is present in less than 50% of cases[6,7]. Only 20-30% of UTB patients will have a previous history of PTB; an additional 25-50% will have radiographic evidence of prior subclinical PTB[16,21]. The intravenous urogram (IVU) remains the gold standard in imaging early renal TB. In spite of the fact that the definitive diagnosis of genitourinary tuberculosis is established by positive results on urine culture or histologic examination, the imaging modalities make an important part of the investigation module. In the initial work-up, plain X-ray abdomen and chest are the two basic imaging tests. Plain X-ray abdomen may show renal calcification. Renal calcification may develop in 7 to 14% of patients.[6] Calcification rarely occurs in ureter (intraluminal), bladder wall, or seminal vesicles. Plain radiographs of chest and spine should be done to detect any pulmonary (active or old healed granuloma) or spinal involvement. Ultrasonography is a poor modality to show morphological changes. It is useful as an office procedure to monitor the degree of hydronephrosis/renal lesions during medical treatment. It also gives information regarding the bladder volume.

Intravenous urography

Among the various imaging modalities, intravenous urography (IVU) has been considered to be one of the most useful tests. IVU provides both anatomical as well as functional details of the kidneys and ureters. The earliest radiographic changes of GUTB may demonstrate changes in the minor renal calyces with loss of sharpness and blunting. Progression of the disease will cause "moth eaten" appearance of the calyces and lost calyx due to infundibular stenosis.

Ureters when involved, these are initially dilated or become irregular in appearance. This is followed by stricture formation with predilection for the infundibulum, ureteropelvic junction, and distal ureter, which are the sites for narrowing. At these states, the ureter looks like beaded or pipestem or even corkscrew configuration. Ten to 56% of the patients develop ureteric strictures.[25] Involvement of ureteric orifices in the late stages, as these become fibrotic and fixed, leads to the development of vesicoureteric reflux (VUR).

Computed tomography (CT scan)

Currently, at many centers, CT is replacing IVU as an imaging modality of choice in GUTB. It is equally good at identifying calyceal and infundibular abnormalities, renal parenchymal destruction, and hydronephrosis or hydroureter. In addition, it identifies adjacent adrenal, retroperitoneal, prostatic, and seminal vesicle abnormalities.[25]

Cystoscopy and biopsy

Cystoscopy is rarely indicated for diagnostic purpose. Biopsy is needed if there is suspicion of malignancy. It should be done only after 4-6 weeks of medical therapy to prevent dissemination of the disease (i.e., tubercular meningitis). The cystoscopic findings are reduced bladder capacity and patulous ureteral orifice. The positive bladder biopsy diagnostic of GUTB can be found in up to 46% of the patients.[22]

Retrograde and antegrade pyelography

There are two indications for it. One is for ureteral catheterization to obtain urine sample for culture for localization of the disease. The other indication being to delineate the stricture of the lower ureter. Percutaneous antegrade access is required if retrograde access is unachievable or insufficient for drainage of the kidney. It also provides a route for obtaining urine samples from the renal pelvis or tuberculous cavities for culture and to assess therapeutic drug concentration at the target sites.[26]

Magnetic resonance imaging (MRI)

Useful in patients with compromised renal function, pregnancy, or allergy to contrast media. It gives good morphological details for the kidneys as well as excellent delineation of the ureters.[27]

Radioisotope studies

Radioisotope studies are useful to determine split renal function and drainage in advanced stage of the disease.

Pathogenesis :

Causative organisms :

MTB, an obligate pathogen, is the usual cause, occasionally, *Mycobacterium bovis*,[27] and *Mycobacterium avium* intracellulare (MAIC). MAIC is transmitted via natural water sources, indoor water systems, pools, and hot tubs,[28-30]and can cause disseminated disease, particularly in immunosuppressed individuals, including renal transplant patients.[31]

Spread of tuberculosis to the urinary tract:

Hematogenous dissemination of MTB occurs from a primary TB focus within the lungs, bone, or other organs and can involve both kidneys.[32] The kidneys, and possibly the prostate and seminal vesicles, are often the primary sites of GUTB. All other genital organs, including the epididymis and bladder, become involved by ascent or descent of MTB from a source elsewhere in the genitourinary tract.[32] In most patients, acquired cellular immunity develops and there is inhibition of bacterial multiplication and containment of the disease by the formation of microscopic granulomas.[36] Healing may also occur as a result of anti-TB chemotherapy administered to control the clinically active focus.In immune-competent patients, these granulomas heal or remain stable for many years.[36]

Re-activation of tuberculosis

If there is a breakdown in host immunity, re-activation or re-infection occurs. One or more tubercles may enlarge after years of inactivity.[39] This latent period varies considerably and may extend from 5 to 40 years.[22,25]

In the kidneys, the bacilli lodge in the periglomerullar capillaries where they form microscopic granulomas, which may later grow into macroscopic granulomas.[39] This occurs bilaterally.

The morphology of the lesions depends on the site of infection, the virulence of the organism, and the immune status of the patient.[40]In immune-competent patients, granulomas are well formed and caseous necrosis is frequently seen. Various types of tuberculous involvement can occur in different areas of the same kidney,[41]or even in both kidneys. However, severe affection is more commonly unilateral. This is one possible cause of delay in patient presentation, leading to irreparable unilateral loss of renal function leading to irreparable unilateral loss of renal function.

Parenchymal changes

The medullary portion of the renal parenchyma is usually spared initially. For unknown reasons, the upper and lower poles of the kidney are more commonly affected than other areas.[17]Cortical granulomas enlarge and coalesce, with the bacilli spilling down the nephrons and getting trapped in the narrow segment of the loop of Henle, establishing new foci of infection within the renal pyramid. These papillary lesions caseate and cavitate, frequently forming ulcero-cavernous lesions as they erode into the pelvicalyceal system (PCS).[35] Extensive papillary necrosis may develop with the formation of frank cavities and destruction of the adjacent renal parenchyma. These may also extend into the collecting system via rupture, or cause parts of the papillae to become necrotic and slough.[36] A mass lesion may result from massive destruction and coalescence of granulomas, if they do not rupture into the adjoining calyx.[37] Alternatively, these granulomas may coalesce and form cavities after liquefaction. Hypercalcemia may occur, usually secondary to abnormal cortisol production by granulomatous tissue. Although calcification is unusual in the early stages of the disease, nearly every end-stage tuberculous kidney contains calcification. Rarely, UTB can present as a well-circumscribed multi-septated cystic renal mass.[38] In immunosuppressed individuals, the granulomas may be less well formed and caseous necrosis is seen less frequently.[27]

Pelvicalyceal system changes

When bacilli are shed into the urine, the disease spreads antegradely to involve the urothelium of the renal pelvis, ureter, bladder and, at times, the adjacent genital tract.[38] Infection in the walls of the calyces, pelvis, and ureter produces significant inflammatory mucosal thickening, a commonly overlooked imaging finding. Single or multiple calyces may be involved in one or both kidneys. Microscopic granulomas may form here too. Ulceration soon follows.

In advanced disease, in addition to loss of parenchyma by caseation, intra-renal scars and strictures lead to obstruction and dilatation of

segments of the PCS. Strictures are more common at sites of normal narrowing, such as the calyceal neck, the pelvi-ureteric junction, and the ureterovesical junction. Early scarring is apparently reversible by appropriate steroid treatment, but end-stage fibrotic strictures are irreversible. Urinary obstruction from strictures along with renal parenchymal caseation destroys all or part of the kidney. The pattern of destruction depends on the relative rates of progression of parenchymal disease and urinary-flow obstruction. Parenchymal caseation, necrosis, and calcification may predominate, which causes the kidney to be destroyed . Alternatively, obstruction may predominate, in which case massive hydronephrosis or hydrocalicosis may be the final stage. TB of the kidney thus reflects competing processes: (a) The destructive effects of the bacilli, leading to ulceration, cavitation, and fistulization and (b) the host's secondary defense and healing mechanism leading to the formation of granulomas along with fibrosis, calcium deposition, and strictures, which may worsen the obstruction causing progressive renal dysfunction.[39] The final outcome is thus extremely variable.[15]Usually, however, both processes occur concurrently and may lead to a non-functioning, calcified kidney of any size; this process is called autonephrectomy. Nephrectomy has been advised to remove the trapped dormant bacilli in such autonephrectomized kidneys.[40]

Tuberculous interstitial nephritis (TIN)

Occasionally, TB can affect the kidney more insidiously, causing TIN which, if untreated, progresses to renal failure. Rupture of the bacilli into the interstitium can lead to isolated interstitial disease, without persistent pyuria, hematuria, or identifiable AFB in the urine, leading to diagnostic dilemmas. Histology reveals chronic tubulointerstitial nephritis, usually with granuloma formation, which may or may not be associated with caseation. With appropriate staining, AFB are identifiable on histology. Evidence of coexisting TB elsewhere may be the only clue to TB being the cause of the falling glomerular filtration rate (GFR). If the diagnosis has been made while useful renal function still remains, it may be possible to arrest the fall in GFR or even produce improvement, using a combination of anti-tubercular treatment and corticosteroids.[40]

Renal failure

The overall incidence of renal failure reported in the literature is 24%. There are three mechanisms by which TB can cause renal failure:

- Renal parenchymal infection causing obliterative endarteritis with extensive dystrophic calcification or secondary renal amyloidosis, both leading to renal impairment.
- Post-obstructive atrophy secondary to multiple strictures.
- Insidious TIN destroying the renal parenchyma. This is a form of culture-negative renal TB. The only clue could be echogenic kidneys on US along with signs of TB elsewhere. Confirmation is usually by AFB staining of histopathology/Fine needle Aspiration Cytology (FNAC) samples.

Renal tuberculosis with other renal diseases/lesions

There have been a number of case reports of TB associated with various forms of glomerulonephritis, including a case report of miliary TB complicated by focal proliferative glomerulonephritis, in which immune deposits were present, but no granulomas.[41]

Complications :

Extra renal spread

The TB disease process may spread to the perinephric and retroperitoneal areas. Fistulas may extend even beyond these confines, including into the gastrointestinal tract, skin, lymphatic vessels, and thoracic cavity (pleura, bronchus).[41] Renal TB causing a liver abscess has been reported.[42]

Amyloidosis

Chronic TB is occasionally complicated by amyloidosis which, in India, is an important cause of renal disease.[21] Prompt treatment of the underlying TB focus can prevent progression to end-stage renal disease.

Squamous metaplasia

Keratinizing squamous metaplasia, which is a potential risk factor for the development of

squamous carcinoma, may develop as a late complication of chronic inflammation and infection of the renal pelvis.[20]

Treatment: Conventional Antituberculosis Medication with Steroids in initial phase. Renal regimen should be followed if kidney function is impaired.[42]

Conclusion:

Bangladesh is a TB burden country and various type of extrapulmonary tuberculosis is increasingly diagnosed day by day due to improved diagnostic technique . On the other hand number of chronic kidney disease patient is also in increasing trend . A good number of CKD patient may be due to tuberculosis but they remain undiagnosed for prolong period and ultimately present as renal failure. High degree of clinical suspicion is required for diagnosis of genitourinary tuberculosis . All the patient of CKD and the patients who have suffered from PTB should be evaluated for GUTB to prevent further damage.

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CASE REPORT

Every Patient with Chronic Cough Should be Evaluated Cautiously

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Abstract:

A 52 years old gentleman presented with chronic cough in early part of 2013. Initially the cough was dry for more than one and half year with no history of shortness of breathing, wheezes haemoptysis or chest pain and was treated symptomatically. But his cough reappeared after an interval of 10 months along with shortness of breath and scanty sputum production and his blood examination reports showed high ESR, chest X-ray revealed bilateral scattered ill defined opacities and was treated with Cat-I ATT (Anti Tubercular Therapy). His condition was deteriorating and was referred in our institute. On chest examination he was found scattered fine crepitations on both lung fields. MT test was found no iduration (00 mm) after 72 hours but raised serum Calcium and ACE (Angeotensin Converting Enzyme) level and BAL (Bronchoalveolar Lavage) fluid cytology revealed lymphocytosis but no fungal hyphae or any gram stained bacteria was found. Based on clinical findings and investigations our final diagnosis was Sarcoidosis, and he was treated with corticosteroid and immunosuppressant. His condition was improved and pulmonary lesions disappeared within a few months.

[Chest & Heart Journal 2014; 38(2) : 116-120]

The Scenario:

In February 2013, a 52 years old man presented with unproductive cough for more than one and half years. He had no history of shortness of breath, wheeze, haemoptysis or chest pain. His clinical examination including chest findings were unremarkable. He was advised for CBC (Complete blood count) with ESR, Serum total IgE and a CXR (Chest X-ray) postero-anterior view and was prescribed montelukast 10 mg and fexophenadine 120mg, each one at every night for one month. His condition was improved and he didn't perform the investigation at that time. After 10 months, the gentleman consulted with another specialist physician due to reappearance of the cough along with scanty sputum production and shortness of breath. On the basis of presentation and radiological findings (ill defined opacities on both lung fields, consistent with bilateral Pulmonary Tuberculosis) he was treated with Cat-I ATT (Anti Tubercular Therapy) for 6 months. His condition was not improved rather gradually deteriorated after Anti Tubercular Therapy.

Finally the gentleman came back to OPD of NIDCH in June 2014. His chest examination had found scattered fine crepitations on both sides of chest which was unaltered with coughing. Laboratory showed high ESR (88 mm in 1sthr), leukocytosis with neutrophylia. His chest X-ray

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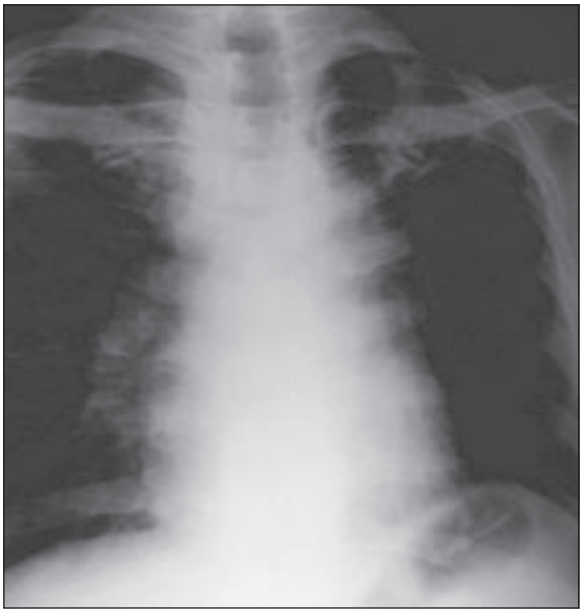
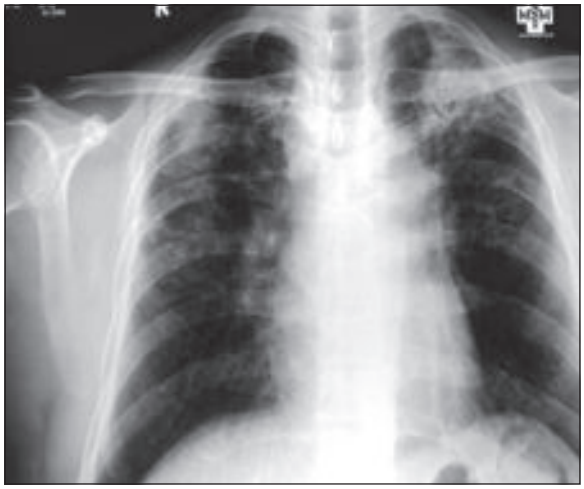
showed bilateral ill defined opacities, CT scan of chest revealed inhomogenous and nodular opacities with fibrosis , more marked in both uppeer lobers along with mediastinal lymphadenopathy.The pattern of distribution, upper lung predominance, and coexistence of mediastinal lymphadenopathy strongly indicate the presence of Sarcoidosis.

His sputum for AFB was negative, sputum for Gene X-part revealed no MTB detected, sputum for fungal hypae was found negative, his MT test revealed 00 mm induration after 72 hours but serum Calcium(9.14 mg/dl) and ACE(88 U/L) level was elevated. CT guided FNAC from Left Lung Lesion revealed inflammatory lesion, FOB also showed inflammatory lesion. BAL for cytology showed lymphocytosis (L-75%) but BAL for fungus, gram stain and AFB showed negative findings. Spirometry revealed moderate restrictive ventilatory defect. His renal and hepatic functions found normal.

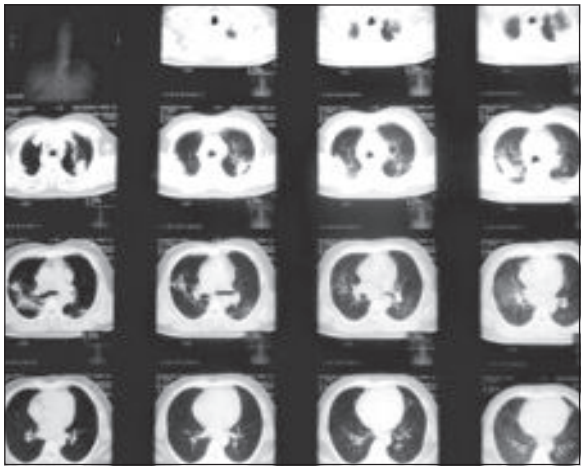
The Chest CT done on June 2014: Inhomogenous and nodular opacities with fibrosis are seen, more marked in both uppeer lobers along with mediastinal lymphadenopathy.The pattern of distribution, upper lung predominance, and coexistence of mediastinal lymphadenopathy strongly indicate the presence of sarcoidosis.

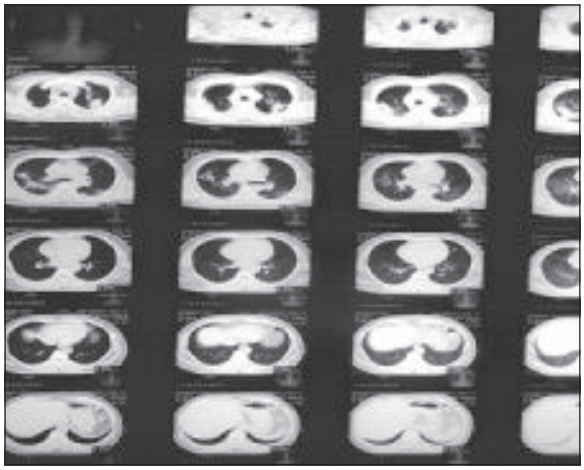


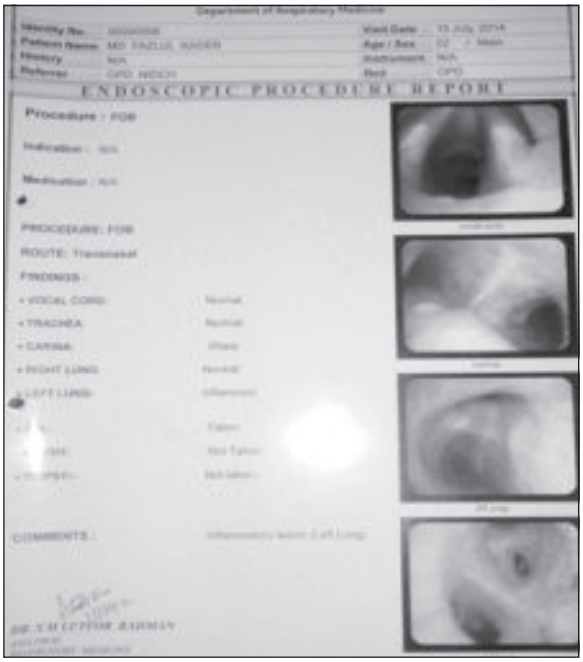
CXR done on 21.12. 2013: Ill defined opacities



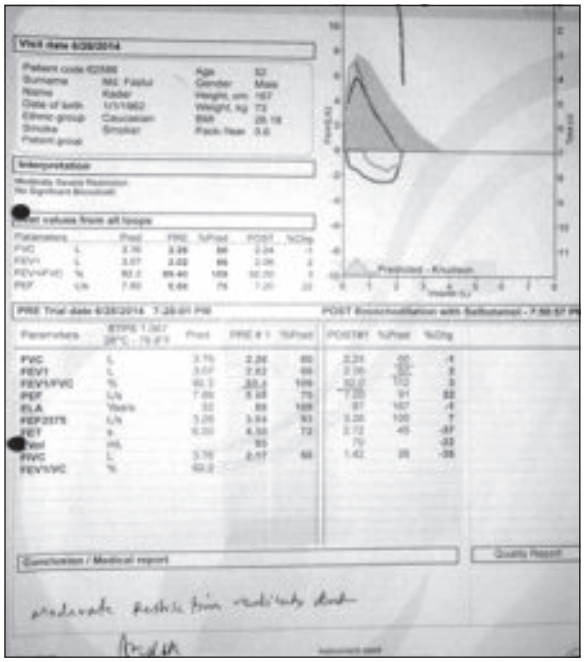
CXR done on 24.06. 2014: The Chest shadow Increased are found on both lung fields







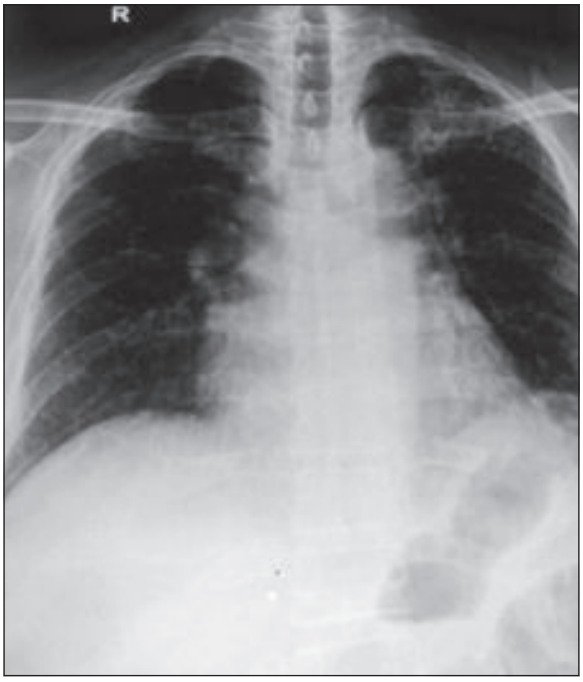
FOB done on 15.07 2014: Inflammatory lesion

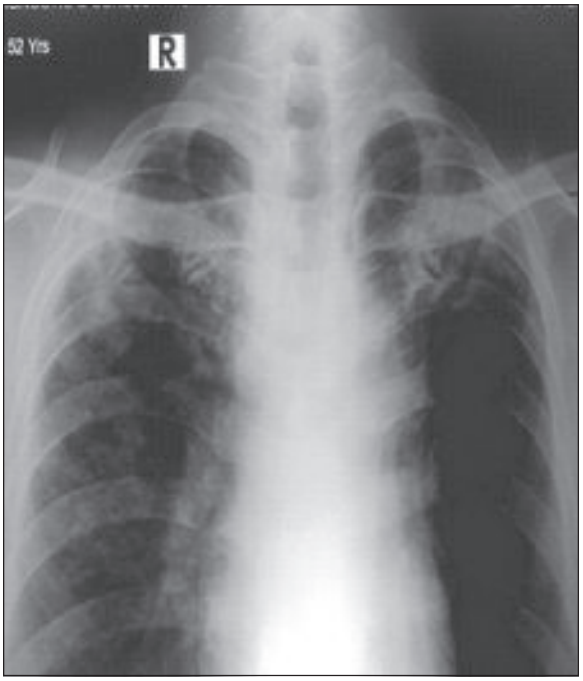


Spirometry done on 28.06 2014: Restrictive ventilatory defect (Moderate)

On the basis of clinical examination and laboratory investigations the patient was diagnosed as a case of Sarcoidosis. He was given prednisolone 40 mg daily in the morning with Azathioprine 50 mg daily at night.

On follow-up after one month, the patient presented with improved all of his symptoms (with no cough or shortness of breath) and his radiological findings improved on subsequent chest X-rays.





Follow-up CXR done on 30.08. 2014 and on 21.12 2014: The Chest shadow almost disappeared.

Discussion:

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized pathologically by the presence of non-caseating granulomas in involved organs. Sarcoidosis most frequently involves the lungs followed by eyes and skin. Presentation as retroperitoneal and lung mass is rare in sarcoidosis.[1] Systemic involvement in sarcoidosis include pulmonary, lymphatic, muscle, hepatic, joint, haematologic, dermatologic, ocular, psychiatric, ranal, splenic, neurologic, nasal sinus, cardiac, bone and oral. Sarcoidosis is thought to be due to an inflammatory response to an environmental antigen in a genetically susceptible person. Hypercalcaemia may occur because vitamin D analogs are produced by activated macrophages. Hypercalciuria may be present, even in patient with normal serum calcium levels.

If Sarcoidosis is suspected, a chest X-ray should be the first test followed by biopsy and exclusion of other granulomatous disease. Chest X-ray tends to assess the severity and extend of the disease to determine whether therapy is indicated.

Exclusion of other diagnosis is critical, because many other disorders and processes can cause granulomatous inflammation. Differential diagnosis of Sarcoidosis is: mycobacterial infections, fungal infections, rheumatologic disorders, hematologic cancer, hypersensitivity and others. Biopsy tissue should be cultured for fungi and mycobacterium. Occupational, environmental and infectious antigens exposure should be explored.

Among the differentials, Mycobacterium Tuberculosis is the most common. For this reason before giving ATT Sputum for AFB and other possible relevant investigations should be done to stablish the diagnosis and it is not wise to start ATT only with seeing the CXR.

Among laboratory testing complete blood count, serum calcium, liver and renal functions, serum ACE levels are important to make the diagnosis. However, ACE levels may be useful for monitoring adherence with corticosteroid treatment. Bronchoalveolar lavage (BAL) is particularly useful to exclude other forms of interstitial lung disease and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes >10%) suggests the diagnosis in the proper clinical context.

Sarcoidosis is thought to be chronic up to 30% of patient, and 10 to 20% experience permanent sequelae. The disease is fatal in 1 to 5% cases due to respiratory failure caused by pulmonary fibrosis and less often due to haemorrhage. Serial prognosis monitoring is recommended in sarcoidosis. In about 90% of patients who have spontaneous remission, remission occurs within the first 2 years after diagnosis; <10% of these patients have relapses after 2 years. Patient who do not experience remission within 2 years are likely to have chronic disease.[2]

Treatment for the patients of sarcoidosis includes NSAIDs to treat musculoskeletal discomfort, corticosteroids for disease modify and occasionally immunosuppressant for patients who are corticosteroid resistant.

A 2002 study in twenty pulmonary medicine departments in Finland stated that immediate treatment of pulmonary stage- II Sarcoidosis but

Table-I

Chest X-ray Staging of Sarcoidosis

Stage	Definition	Incidence of Spontaneous Remission
0	Normal chest x-ray	—
I	Bilateral hilar, paratracheal, and mediastinal lymph adenopathy without parenchymal infiltrates	60-80%
II	Bilateral hilar and mediastinaladenopathy with interstitial infiltrates (usually in upper lung)	50-65%
III	Diffuse interstitial infiltrates without hilaradenopathy	<30%
IV	Diffuse fibrosis, often associated with fibrotic-appearing conglomerate masses, traction bronchiectasis	0%

not stage I disease improve the 5 years prognosis with regard to lung function variables.[3] Oral prednisolone for 3 months followed by inhaled budesonide for 15 months (800 microg bid) was given. However, after 5 year follow-up, 26% steroid treated patients still had remaining chest radiographic changes.

Inhaled corticosteroids can relieve cough in patients with endobronchial involvement. Tropical corticosteroid may be useful in dermatologic, nasal sinus and ocular disease.

Organ transplantation is an option for patients with end-stage pulmonary, cardiac, or liver involvement, although disease may recur in the transplanted organ. A significant proportion of sarcoidosis patients have disease recurrence after lung transplantation and presence of active granulomas on explant is associated with subsequent recurrence.[4]

Summary points

- Systemic and extrapulmonary involvements are common with sarcoidosis. But >90% of adult patients have pulmonary involvement.
- Obtain a chest imaging study but confirm the diagnosis by biopsy, usually endobronchial ultrasound guided transbronchial needle aspiration of a mediastinal or hilar lymph node.
- Assess pulmonary severity with pulmonary function testing and exercise pulse oximetry.
- Test for extrapulmonary involvement with ECG, slit-lamp examination, renal and hepatic function tests, and serum and urinary Ca testing.
- Treat patients with systemic corticosteroids when indicated (eg. Severe symptoms, hypercalcaemia, progressivedecline in organ function, cardiac and neurologic involvement).
- Treat with immunosuppressants if patient cannot tolerate moderate doses of corticosteroids, sarcoidosis is resistant to corticosteroids, or corticosteroids are required long time.
- It is not wise to start ATT only with seeing the CXR as many other similar presentations are available.
- It is wise to refer the respective cases to specific specialist for proper management.

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CASE REPORT

A Case of Intestinal Tuberculosis

Taufiqul Haque[1], Selina Aktar[2], Atiqur Rahman[3], Jalal Mohsin Uddin[4], Habiba Khatun[5]

Abstract:

Tuberculosis can involve any part of the gastrointestinal tract and abdominal TB is the sixth most frequent site of extrapulmonary involvement. Tuberculosis bacteria reach the gastrointestinal tract via haematogenous spread, ingestion of infected sputum, or direct spread from infected contiguous lymph nodes and fallopian tubes. The gross pathology is characterized by transverse ulcers, fibrosis, thickening and stricturing of the bowel wall, enlarged and matted mesenteric lymph nodes, omental thickening, and peritoneal tubercles.

Peritoneal tuberculosis occurs in three forms : wet type with ascitis, dry type with adhesions, and fibrotic type with omental thickening and loculated ascites. The most common site of involvement of the gastrointestinal tuberculosis is the ileocaecal region. Ileocaecal and small bowel tuberculosis presents with a palpable mass in the right lower quadrant and/or complications of obstruction, perforation or malabsorption especially in the presence of stricture.

Chest X-rays show evidence of concomitant pulmonary lesions in less than 25 per cent of cases.Useful modalities for investigating a suspected case include small bowel barium meal, barium enema, ultrasonography, computed tomographic scan and colonoscopy.

Laparoscopy is a very useful investigation in doubtful cases. Management is with conventional antitubercular therapy for at least 6 months. The recommended surgical procedures today are conservative and a period of preoperative drug therapy is controversial.

Key words: *Abdominal tuberculosis - extrapulmonary - gastrointestinal , peritoneal TB.*

[Chest & Heart Journal 2014; 38(2) : 121-124]

Introduction:

Abdominal tuberculosis is uncommon in developed countries, although an increase in this disease has been noted in immigrants from countries with a high prevalence of tuberculosis and in AIDS patients Abdominal tuberculosis (TB) is the sixth commonest extra-pulmonary TB. TB can spread to the peritoneum through the gastrointestinal tract via mesenteric lymph nodes or directly from the blood, lymph, and fallopian tubes.[1,2] Malignancy and TB may mimic each other leading to misdiagnosis. Ascites of tuberculous peritonitis (TBP) is in exudative form and may commonly be misdiagnosed as carcinomatous peritonitis, especially in the elderly.

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Here we present a case of intestinal tuberculosis in a 18 years young lady. Early recognition and proper treatment with Antitubercular drugs can prevent complications.

Case Report:

Miss Nahar 18 years un-married lady admitted in our Hospital with complaints of pain in whole abdomen for 3-4 months, low grade fever for one month, burning sensation during micturition for 6 days. On admission her condition was poor, vitals ok. Per abdominal examination revealed a large about 9x10 cm intra-abdominal lump , mostly in the RIF , with ill-defined margin and fixed.

Investigation reports shows Hb-8.6 gm/dl,ESR-45mm in ist hr,WBC-8200/cmm of blood.Blood sugar-normal , USG shows a cystic lesion of 9.2x11.5 cm is noted at the right side of pelvis which cannot be separated from rt ovary, with moderate ascites & left sided pleural effusion.

CA-125—602.37U/ml.Tuberculin skin test(MT test) was negative & sputum smears were negative for AFB.She was adviced for CT scan of whole abdomen , as the patient was very poor she cannot afford this. Chest X-ray shows left sided mild pleural effusion, but pleural fluid aspiration was dry tap.

A diagnostic laparotomy was done, approximately 1000 ml serosanguineous ascetic fluid was sucked out.few ml of fluid send for cytological examination.Greater omentum found studded with neumerous whitish tubercles resembling omental cake (Figure-1) & it was was wrapped around the small intestine. Multiple small whitish tubercles were present all over the inlammed small intestine(Figure-2). Biopsies were taken from the greater omentum &the mesentry. Cytologic fluid found negative for malignancy. All biopsy reports show caseating and non-caseating tuberculous granulomas. So now she was diagnosed as a case of intestinal tuberculosis and treated with anti-tubercular drugs. On the sixth post-operative day, she was put on oral antitubercular therapy (rifampicin, isonaizid, ethambutol and pyrazinamide). She was discharged on the 12th day following surgery. In follow-up after two months, the patient was doing well without encountering any complications.

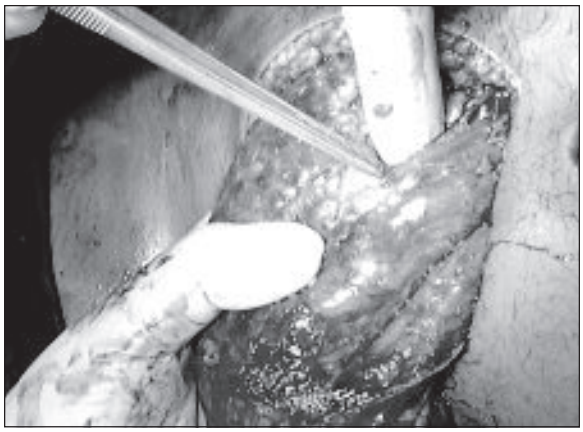

Fig.-1: *Greater omentum shows thickening &studded with multiple whitish tubercles.*

Fig.-2: *Small intestine shows inflammation , thickening &wrapped with multiple*

Discussion:

Tuberculosis (TB) can involve any part of the gastrointestinal tract from mouth to anus, the

peritoneum and the pancreatobiliary system. It can have a varied presentation, frequently mimicking other common and rare diseases .TB of the gastrointestinal tract is the sixth most frequent form of extra-pulmonary site, after lymphatic, genitourinary, bone and joint, miliary and meningeal tuberculosis.[3]

The postulated mechanisms by which the tubercule bacilli reach the gastrointestinal tract are: (*i*) hematogenous spread from the primary lung focus in childhood, with later reactivation; (*ii*) ingestion of bacilli in sputum from active pulmonary focus; (*iii*) direct spread from adjacent organs; and (*iv*) and through lymph channels from infected nodes.

Abdominal TB is defined as infection of the peritoneum, hollow or solid abdominal organs with mycobacterium tuberculosis.[4] The natural course of intestinal TB follows three patterns: ulcerative, hypertrophic, and ulcerohypertrophic. In the ulcerative form, transverse ulcer occurs perpendicular to the bowel axis and may bleed, perforate, or form fistulas. In the less common hypertrophy form, a mass or multiple nodules, with or without caseous or necrosis forms that may mimic malignant neoplasms such as lymphoma or carcinoma, may cause obstruction.

Tuberculous granulomas are initially formed in the mucosa or the Peyer's patches. These granulomas are of variable size and characteristically tend to be confluent, in contrast to those in Crohn's disease. Granulomas are often seen just beneath the ulcer bed, mainly in the submucosal layer. Tubercular ulcers are relatively superficial and usually do not penetrate

beyond the muscularis. They may be single or multiple, and the intervening mucosa is usuallyuninvolved. These ulcers are usually transversely oriented in contrast to Crohn's disease where the ulcers are longitudinal or serpiginous.[5] Cicatrical healing of these circumferential 'girdle ulcers' results in strictures. Occlusive arterial changes may produce ischaemia and contribute to the development of strictures.[6]

The most common site of involvement is the ileocaecal region, possibly because of the increased physiological stasis, increased rate of fluid and electrolyte absorption, minimal digestive activity and an abundance of lymphoid tissue at this site. The frequency of bowel involvement declines as one proceeds both proximally and distally from the ileocaecal region.[7,8]

Peritoneal involvement may occur from spread from lymph nodes, intestinal lesions or from

tubercular salpingitis in women. In tuberculous peritonitis, the peritoneum is studded with multiple yellow-white tubercles. It is thick and hyperaemic with a loss of its shiny luster.

The omentum is also thickened.[9]

Abdominal lymph nodal and peritoneal tuberculosis may occur without gastrointestinal involvement in about one third of the cases .Peritoneal tuberculosis occurs in 3 forms: (*i*) Wet type with ascitis; (*ii*) Encysted (loculated) type with a localized abdominal swelling; and (*iii*) Fibrotic type with abdominal masses composed of mesenteric and omental thickening, with matted bowel loops felt as lump(s) in the abdomen. A combination of these types are also common.[3]

Peritoneal TB and primary peritoneal carcinoma can both present as an abdominal mass and ascites with elevated serum CA125 and should therefore be considered as a differential diagnosis, especially for young women.[10] Before the discovery of effective medical therapy for TB (TBMT) there was no hope for recovery of patients with abdominal TB. Reactive fibrosis of the peritoneum and formation of adhesions with adjacent tissues account for the low incidence of perforation (0% to 11% in adults, 3% to 4% in children, 2.5% to 6% at autopsy, and 20% of all non-appendiceal perforations) reported in literature.[11]

Abdominal cocoon, also known as sclerosing encapsulating peritonitis (SEP), which is a rare condition that is characterized by the encasement of the small bowel by a fibrocollagenic cocoon-like sac. TB is an infrequently implicated cause of abdominal cocoon, and has only occasionally been reported previously in the literature.[12,13]

Malignancy and TB may mimic each other, leading to misdiagnosis. Ascites of tuberculous peritonitis (TBP) is in exudative form and may commonly be misdiagnosed as carcinomatous peritonitis, especially in the elderly. Since the clinical manifestations of peritoneal tuberculosis may resemble those of ovarian carcinoma with ascites, abdominopelvic masses, and elevated CA 125, a number of women with this disease are first seen by a gynecologist.[14]

Abdominal tuberculosis is predominantly a disease of young adults. Two-thirds of the patients are 21-40 yr old and the sex incidence is equal, although some Indian studies have suggested a slight female predominance.[6]

The clinical presentation of abdominal tuberculosis can be acute, chronic or acute on chronic. Most patients have constitutional symptoms of fever (40-70%), pain (80-95%), diarrhoea (11-20%), constipation, alternating constipation and diarrhoea, weight loss (40-90%), anorexia and malaise. Pain can be either colicky due to luminal compromise, or dull and continuous when the mesenteric lymph nodes are involved.[3]

Tuberculous lymphadenitis can mimic malignancy, especially when adherent to adjacent organs. PCR test of the biopsy specimen provides a faster, alternative route for diagnosis with high specificity.[15]

Chest X-ray: Evidence of tuberculosis in a chest Xray supports the diagnosis but a normal chest X-ray does not rule it out.[16] *Plain X-ray abdomen*: Plain X-ray abdomen may show enteroliths, features of obstruction *i.e*. dilated bowel loops with multiple air fluid levels, evidence of ascitis, perforation or intussusception.

Small bowel barium meal & Barium enema shows various features in cases of chronic form of gastrointestinal TB. Barium studies though accurate for intrinsic bowel abnormalities, do not detect lesions in the peritoneum. Ultrasonography is very useful for imaging peritoneal tuberculosis.[17]

Radiologists should be knowledgeable about this rare entity to aid in making a definite diagnosis, which is best made on computed tomography, and thus help in the management of these patients.[18] Ileocaecal tuberculosis is usually hyperplastic and well evaluated on CT scan. In early disease there is slight symmetric circumferential thickening of caecum and terminal ileum. Later the ileocaecal valve and adjacent medial wall of the caecum is asymmetrically thickened. In more advanced disease gross wall thickening, adherent loops, large regional nodes and mesenteric thickening can together form a soft tissue mass centered around the ileocaecal junction.[19]

Mesenteric disease on CT scan is seen as a patchy or diffuse increase in density, strands within the mesentery, and a stellate appearance. Lymph nodes may be interspersed. Omental thickening is well seen often as an omental cake appearance.

Colonoscopy is an excellent tool to diagnose colonic and terminal ileal involment but is still often

Underutilized.[20,21]

Currently laparoscopy is also used as diagnostic method in acute abdomen conditions to rule out malignancy or tuberculosis by taking tissue biopsy.[18]

All patients should receive conventional antitubercular therapy for at least 6 months includinginitial 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol.[22] The surgical procedures of intestinal tuberculosis are conservative, such as bypassing the stenosed segment, strictureplasty, a segment of bowel bearing multiple strictures or a single long tubular stricture may require resection and anastomosis.[23]

Conclusion:

Abdominal tuberculosis is defined as infection of the peritoneum, hollow or solid abdominal organs with *Mycobacterium tuberculi*. The peritoneum and the ileocaecal region are the most likely sites of infection and are involved in the majority of the cases by hematogenous spread or through swallowing of infected sputum from primary pulmonary tuberculosis. Pulmonary tuberculosis is apparent in less than half of the patients. Patients usually present with abdominal pain, is usually made through a combination of radiologic, endoscopic, microbiologic, histologic and molecular techniques. Antimicrobial treatment is the same as for pulmonary tuberculosis Surgery is occasionally required.

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CASE REPORT

A Young Lady with Undifferentiated Connective Tissue Disease and ILD-A Case Report

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Abstract:

As much as 25 percent of rheumatic disease patients with systemic symptoms cannot be definitively diagnosed.[1,2] Such patients were first described as having "collagen" or "connective tissue" diseases, since they shared similar clinical and pathologic features of widespread inflammation.[3-5] Subsequently, these patients have been considered to have diffuse or undifferentiated (or sometimes early undifferentiated) connective tissue diseases (UCTD).[6] Undifferentiated connective tissue disease is thought to be a kind of connective disease which shows few clinical and serological features of autoimmune connective tissue disease but does not fulfill the diagnostic criteria of well-defined connective tissue disease like rheumatoid arthritis, SLE, systemic sclerosis etc. Though the prognosis of UCTD is excellent but occasionally it is aggressive and may affect lung, brain and kidneys.

Keywords: *Connective tissue diseases, ILD.*

[Chest & Heart Journal 2014; 38(2) : 125-128]

Introduction:

The term "undifferentiated connective tissue disease" (UCTD) is used to describe people who have symptoms and certain lab test results that look like a systemic autoimmune disorder or connective tissue disease. But they don't have enough of such characteristics to meet the diagnosis for a well-defined connective tissue disease, such as rheumatoid arthritis, lupus, or scleroderma.[7] Although the word "undifferentiated" sounds vague, rheumatologists describe this term as real problem. Patients with UCTD have an excellent prognosis. Almost all studies to date indicate a low likelihood of progression to any involvement of organs such as the kidney, lungs, and brain. A small minority of patients (<20%) go on to develop a well-defined connective tissue disease. In a substantial proportion of patients, the disease is mild and no treatment is needed. Rarely, in some people, the symptoms can go away completely. The majority of patients can be treated symptomatically, and very few patients ever require the use of immunosuppressive medications.

Case Report:

A 18 years old young lady, non-diabetic, non-hypertensive admitted in NIDCH on 20.10.2013 with the complaints of severe breathlessness with cough for 20 days, weakness of lower limbs for 6 months, thickening of skin for 1 year. She gave history of Raynaud's phenomenon for 1½ years (Figure-1) and nonspecific arthralgia for same duration without joint swelling and deformity. She also complained of itching on face on exposure to sun light. She noticed thickening of skin in hands, part of forearms, feet, part of legs. She gave no history of difficulty in swallowing. Before 1 year she developed unproductive cough and breathlessness. The breathlessness was initially exertional but now-a-days she is breathless even at rest. She also complained of weakness of lower

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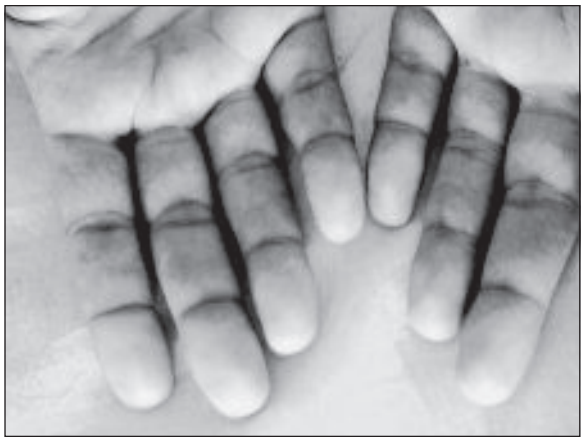

Fig.-1: *Raynaud's phenomenon*

limbs in the form of standing from sitting position. She denied any contact with tubercular patients. She took few antibiotics, bronchodilators in oral form and analgesics in different occasions.

On general examination she was dyspnoeic but alert, conscious and co-operative. Her pulse was 90/m in, B.P-100/80 mm of Hg. Digital clubbing, thickening of skin up to elbows in upper limb and up to knees in lower limbs and hypertrichosis were present. There were malar rash and heliotrope rashes on face and upper eyelids. Examination of chest revealed, chest movement was restricted and total chest expansibility was 3 cm. There were bibasilalar endinspiratory fine crepitations which were unaltered with cough. Examination of cardio-vascular system revealed palpable p2 with presence of left parastarnal heave and accentuated pulmonary component of 2^{nd} heart sound. Examination of upper limbs revealed digital clubbing, Raynaud's phenomenon without digital ulceration. Muscle power of lower limbs were 4/5 bilaterally. Examination of other systems revealed no abnormalities. At this stage our provisional diagnosis was ILD with pulmonary hypertension with mixed connective tissue disease and differential diagnosis were ILD with PH with SLE or Systemic sclerosis or Darmatomyositis.

Investigations: revealed normal CBC. ESR was 50 mm in 1^{st} hour. Biochemical investigations and serum electrolytes were normal, MTB was not detected in sputum for gene x-pert examination. Sputum, blood and urine culture yielded no organism. Tuberculin test was 6mm. She was functionally euthyroid. ABG analysis revealed type-I respiratory failure. ANA was positive but anti-ds-DNA, CRP, RA factor, anti-CCP antibody, anti-SM antibody, cANCA, pANCA were negative. SGOT, SGPT, CPK, 24 hours urinary total protein were within normal limit. X-ray chest (Figure-2) showed bilateral raticulonodular shadow more prominent on lower zones. The patient was further evaluated with HRCT of chest (Figure-3), which also revealed ILD. Echo with color doppler showed pulmonary hypertension, TR (Grade-I), right atrial and venteicular hypertrophy.USG of whole abdomen revealed no abnormalities. 6 minutes walk test showed SpO_2 at baseline 92%, at the end of test 82% which returned to 92% after rest. Spirometry also showed restrictive pattern. At that period we had to apply the ACR's diagnostic criteria of SLE, SS, Darmatomyositis and Acron-Segovia's diagnostic criteria of MCTD. But our findings did not fulfill any criteria. So we had to think of undifferentiated connective tissue diseases and our findings were also consistent with UDCTD.

Patient was treated with oxygen inhalation, frequent nebulization, antibiotics to control infection. Inj. Hydrocortison was given initially which was later

Replaced by oral prednisolone . Deltiazem was added for Raynaud's phenomenon. She was also given antimalarial drug for immunomodulation.

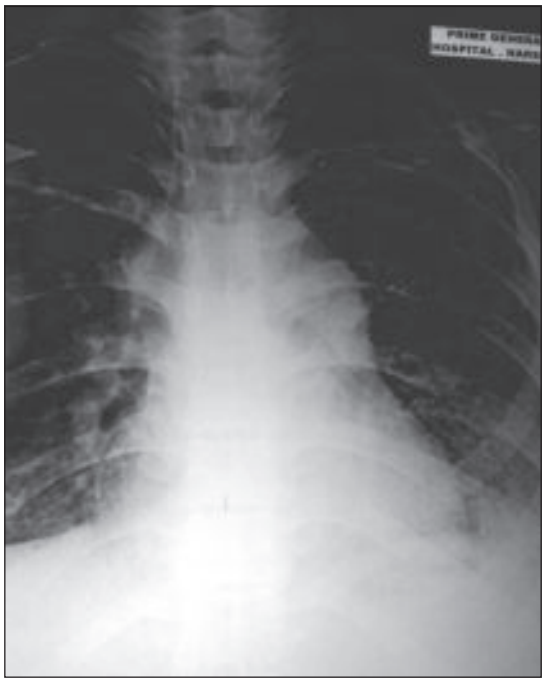

Fig.-2: *Chest X-Ray PA view.*

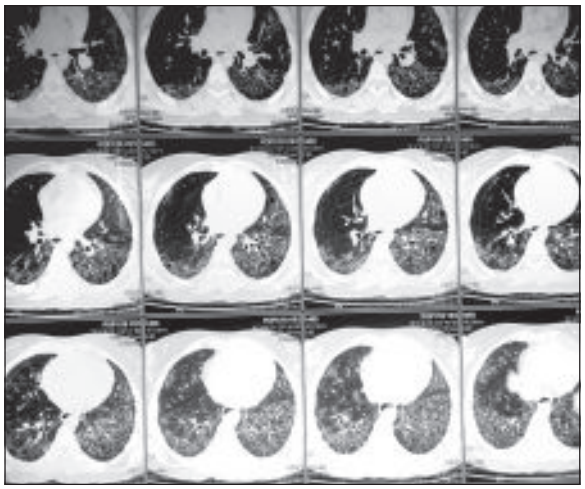

Fig.-3: *HRCT of Chest.*

Discussion:

The term "undifferentiated connective tissue disease" (UCTD) is used to describe people who have symptoms and certain lab test results that look like a systemic autoimmune disorder or connective tissue disease. But they don't have enough of such characteristics to meet the diagnosis for a well-defined connective tissue disease, such as rheumatoid arthritis, lupus, or scleroderma.[7] The term undifferentiated connective tissue disease was first used in 1980's to identify people who were recognized as being in the early stages of a connective tissue disease (CTD) but who did not yet meet the standard criteria for a well-defined CTD. The actual cause of UCTD, like many rheumatic diseases, is not well understood. It is presumed that many of the same immunologic mechanisms that play a role in lupus and rheumatoid arthritis may be involved. The most common symptoms of UCTD are: arthralgia, arthritis , rashes, usually on the face, which can worsen due to sun exposure; alopecia, Raynaud's phenomenon, oral ulcers , xerophthalmia , xerostomia ; low-grade fever ; photosensitivity . Some people also develop pleuritis or pericarditis, neuropathy. The overwhelming majority of people with UCTD do not develop major organ damage. Undifferentiated rheumatic diseases generally comprise one or more of the following clinical scenarios:

- Early Raynaud phenomenon alone.
- Early inflammatory polyarthritis that does not fulfill ACR's criteria for the diagnosis of rheumatoid arthritis.
- Nonspecific rash resembling the cutaneous findings found in defined rheumatic diseases, often associated with an interface dermatitis (i.e, inflammation at the dermal-epidermal junction) .
- Patients who, despite manifesting serologic abnormalities, do not meet ACR criteria for the diagnosis of a specific rheumatic disease.
- Laboratory Findings:

A. Immunologic

- While most studies note that the majority of patients with UCTD are have antinuclear antibodies (ANA), a broad range of immunologic abnormalities can be seen in people with UCTD. These may include: antiphospholipidantibodies, hypergamma-globulinemia, hypocomple-mentemia, a false positive blood test for syphilis, known as "RPR", positive evidence of other markers of autoimmune disease, such as anti-dsDNA antibody, anti-Ro/SSA, anti-SM (Smith), anti-RNP, rheumatoid factor (RF).

B. Hematologic:

Several blood disorders - thrombocytopenia, leukopenia, and anemia - may also occur in patients with UCTD. They are rarely severe enough to require treatment alone. Most therapies are symptomatic and include:

1. Analgesics (such as acetominophen) and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen for musculoskeletal symptoms, such as joint and muscle aches or pains;

2. Topical corticosteroids (creams, lotions or gels that have anti-inflammatory action) and anti-malarial pills such as hydroxychloroquine for skin and mucous tissue symptoms. (Antimalarials have been found to modify immune system function.) For symptoms that don't respond to these drugs, occasionally low dose corticosteroids in pill form (such as prednisone) is recomended for short periods of time. High doses of corticosteroids, cytotoxic agents such as cyclophosphamide, and immunosuppressives such as azathioprine are almost never used. Patients with UCTD have an excellent prognosis. Almost all studies to date indicate a low likelihood of progression to any involvement of organs such as the kidney, lungs,

and brain. It is currently believed that less than 20% of patients with UCTD go on to develop a definite connective tissue disease. As many as one-third will experience a remission of their symptoms. The rest continue with generally mild disease in the undifferentiated form.

Conclusion:

We often ignore the non-specific arthritis, rashes and serological findings all of which are the components of UCTD. Though the prognosis of UCTD is excellent but rarely it may be aggressive as happened in our case. So it is necessary to be careful about UCTD.

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Vol. 38, No. 2, July 2014

CASE REPORT

Surgical Management of Thymoma with Myasthenia Gravis: A Case Report

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Abstract:

Thymoma is a rare tumor with a largely indolent growth pattern. It does, however, have malignant potential as a result of its ability to invade locally and metastasize regionally. Often associated with a number of immune and non immune-mediated paraneoplastic syndromes, patient outcomes are directly related to stage of disease and the ability to achieve a complete surgical resection. Surgery is the mainstay of treatment. We present a case of thymoma followed by a general discussion with an emphasis on surgical treatment along with long term medical management.

Key words: Thymoma, Myasthenia gravis, Surgery.

[Chest & Heart Journal 2014; 38(2) : 129-132]

Introduction:

Thymoma is the most common tumour of the anterior mediastinum. This tumour is associated with unique paraneoplastic syndrome, such as myasthenia gravis (MG), hypogammaglobunemia, and pure red cell aplasia.[1] Accumulated experience suggests that 5-15% of patient with MG are found to have thymomas, while 30-50% of thymomas are associated with clinical MG. Notably, the disease may develop later, even following thymoma resection, if it is not present at the time of discovery of the thymic tumour. So it is essential that a complete thymectomy be performed as part of resection of any anterior mediastinal tumour that may represents a thymoma.[2] MG is a relatively rare auto immune disorder of peripheral nerves in which antibodies form against acetylcholine (Ach) nicotinic post synaptic receptors at the myoneural junction. A reduction in the number of Ach receptors results in a characteristic pattern of progressively reduced muscle strength with repeated use of the muscle and recovery of the muscle strength following a period of rest.[3] Its relationship to thymoma and treatment by thymectomy appear to be related to the role of the thymus in the creation of this antibodies.[4]

Case Report:

A 28 yrs old male university student admitted on 28.12.2013 in Al-Helal specialized hospital, Dhaka with the complaints of dropping of both upper eyelid, respiratory distress and generalized weakness for the last 1 year and a history of respiratory failure relieved by 16 days of

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mechanical ventilation support in an another hospital 2 months back . Physical examination revealed regular pulse 80 beats/min, blood pressure 120/80 mm of Hg. The complete blood count was normal and C- reactive protein level was negative. His Plasma Creatinine was 1.1 mg/dl and the Urea was 4.2 mmol/L; plasma electrolyte and urine analysis were normal. His á-fetoprotein (AFP), â-human chorionic gonadotropin (â-hCG), and lactic dehydrogenase (LDH) level were within normal limit. Anti acetylcholine receptor antibody level were elevated (5 nmol/L).

The electrocardiogram and Transthoracic echocardiography were normal. Loss of the normal anterior clear space on the lateral film of a routine chest radiogram was detected. Repetitive nerve stimulation test showed significant muscle fatigability. Lung function test (spirometry) revealed reduced vital capacity with significant restriction.Computed tomogram (CT) of the chest showed a well-circumscribed, solid anterior mediastinal mass suggestive of thymoma.

The patient was operated on 30.12.2013. Under general anesthesia, with all aseptic precautions standard median sternotomy was done. Thymus was found enlarged, nodular and firm in consistency. Adhesion of thymic tissue with right pleura was present. No other abnormality was detected. Complete resections of thymus with part of adherent pleura were done (figure-1). Thymus (figure-2 and figure-3) was sent for histopathological study. After achieving haemostasis chest was closed leaving two mediastinal chest drain (retrosternal 32 Fr and right pleural 32 Fr) tubes attached with underwater seal drain bags. The patient was shifted to the intensive care unit and was extubated on the same day. Patient was advised to take Acetylcholinesterase inhibitor pyridostigmine (60 mg 4 times daily) and immunosuppressive drugs prednisone (5 mg twice daily) and azathioprine (50 mg twice daily). Patient shifted to general ward on the 2nd post operative day. Histopathology of resected specimen revealed thymoma with area of hyalinization and calcification. Patient discharged home on the 10th postoperative day with advice of taking oral pyridostigmine and azathioprine life long. The patient remains asymptomatic on the subsequent follow up with significant resolution of preoperative symptom.

Fig.-1: *Anterior mediatinum after complete resection of thymus.*

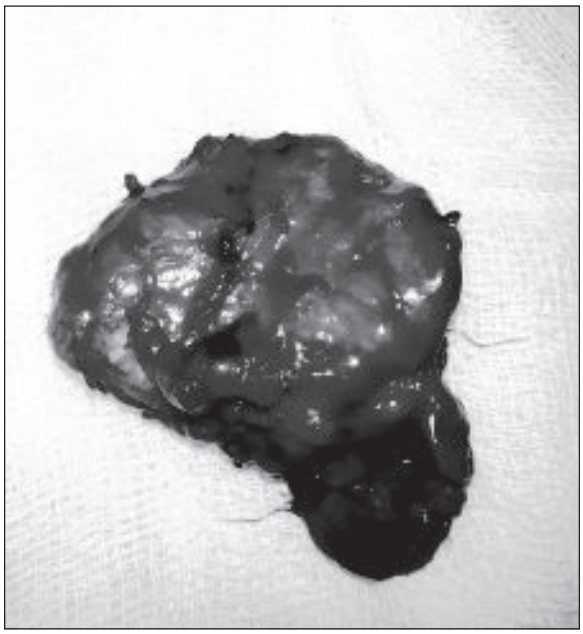

Fig.-2: *Thymus with part of pleura.*

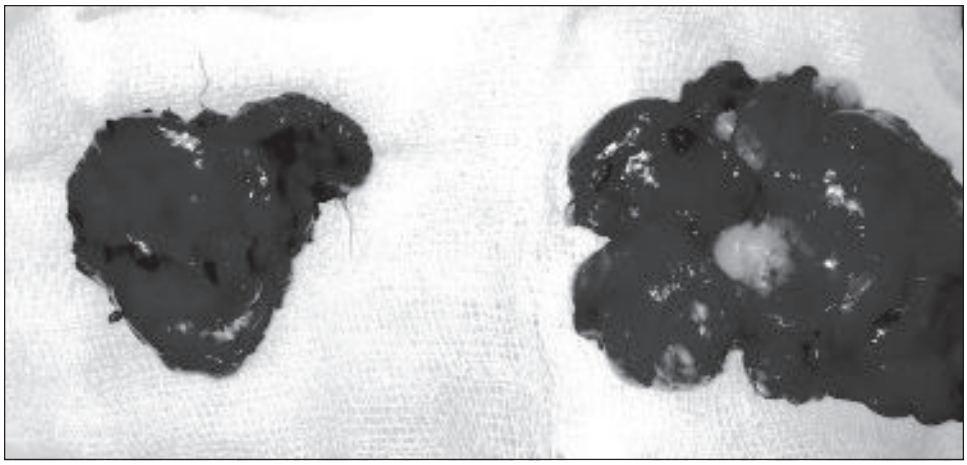

Fig.-3: *Thymic mass.*

Discussion:

Thymoma is an uncommon tumour, but known for its association with the neuromuscular disorder myasthenia gravis (MG).[1] A relationship between MG and thymomas was determined incidentally in 1939 when Blalock and coworkers reported the first excision of a thymic cyst in a 19-year-old girl with MG.[5] The estimated prevalence of MG is approximately 20 cases per 100,000 population in USA with the disease affecting twice as many women as men. However, in older age groups, men are affected more often and the disease is often misdiagnosed.[6] Ocular complications are the most common in first year and are the presenting symptom in 50% of cases often within 1year. Patient have generalized weakness or fatigue and one third of patients develop respiratory weakness, requiring mechanical ventilation.[7] Our patient also had similar types of symptoms and was in mechanical ventilator support for 16 days for respiratory weakness.

The Myasthenia Gravis Foundation of America (MGFA) formed a clinical classification of symptoms of MG.[8] This classification divides MG into 5 main classes and several subclasses. On physical examination, our patient was diagnosed as class ll(b), which reveals moderate severe generalized myasthenia with ocular involvement and mild bulbar symptoms.

In thymoma, there are areas within lymphoid tissue where B-cells interact with helper T-cell to produce antibodies. As the thymus is the central organ for immunological self-tolerance, it is reasonable to support that thymic abnormalities cause the breakdown in tolerance that an immune mediated attack on AChR in MG.[9]

One-third to one-half of all patients with thymoma, the mass is identified in chest X-ray or on CT scan performed for an unrelated problem. CT scan is generally performed to estimate the size and extent of the tumour.[10] Our patient also supports this data.

The anti-acetylcholine receptor (AChR) antibody test for diagnosis of MG has highly specificity up to 100%. A study showed that AChR is positive in 67% of patient with generalized MG and 44% of those with ocular MG.[11] our patient's AChR level also high (5 nmol/L).

Acetylcholine esterase (AChE) inhibitors and immunomodulating therapies are the mainstay of treatment in MG. In milder form of the disease, AChE inhibitors are used initially. These agents include pyridostigmine, neostigmine and edrophorium. Pyridostigmine is used for maintenance therapy.[12] Limited evidence for randomized controlled trails (RCTs) suggest that corticosteroid therapy provides a short-term benefit in MG; this supports the conclusion of previous observational studies as well as expert opinion. A systemic review found no clear difference between steroids and immunoglobulin or azathioprine.[13] our patient also treated with pyridostigmine , steroids and azathioprine in both pre and post operative periods with better result which support this data.

Initial management in most cases of thymoma is surgical. Thymectomy has been proposed as the first-line therapy in most patients with generalized MG.[14] thymectomy not recommended in patient with antibodies to muscle-specific kinase (MusK), because of the typical thymus pathology, which is very different from the more common type of MG characterized by seropositivity for AChR antibodies.[15] MusK was not done to our patient due to unavailability but seropositivity for AChR antibodies was present and patient underwent thymectomy.

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CASE REPORT

Acute Lower Limb Ischemia in a Case of Ischemic and Valvular Heart Disease Patient: A Case Report

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Abstract:

A female patient with valvular heart disease and atrial fibrillation presenting with acute both lower limbs ischemia, had under gone successful embolectomy through bi-femoral approach 16 hours after onset of symptoms. After operation patient was recovered well and patient's both lower limbs were saved. Patient was discharged from hospital on 10th post operative day. Coronary artery bypass graft & double valve replacement operation of same patient was done successfully after two months of embolectomy.

Keywords: *Valvular heart disease, saddle thrombus, aortic occlusion, acute lower limb ischemia, embolectomy.*

[Chest & Heart Journal 2014; 38(2) : 133-135]

Introduction:

Sudden occlusion of the aortic bifurcation by a "saddle" embolus is an uncommon, but well-recognized, complication of mitral stenosis. Acute aortic occlusion is most commonly due to an embolus or thrombus obstructing distal arterial blood flow.[1] The differentiation between embolus and thrombus can be difficult, but atrial fibrillation is viewed as a reliable discriminator.[2] Three quarters of arterial emboli are of cardiac origin primarily due to atrial fibrillation and myocardial infraction.[3] Acute arterial ischemia is caused by emboli or by acute thrombosis superimposed on a chronic underlying partial obstruction. Emboli can be of cardiac or noncardiac origin. 80% of all emboli originated from the heart, the majority of these being of left atrial origin in patients with rheumatic heart disease and atrial fibrillation.[4] The final lodging place of an embolus correlates with the narrowing at bifurcations, laminar blood flow, and the origin of the embolus.[3] Many large emboli lodge at the aortic bifurcation, the first major narrowing of the aorta.[3] Studies by the Panetta and by Elliott reported that 25% of emboli lodge in the aortoiliac area.[2,3] Low-risk patients who present with ischemia of less than 8- hour duration should have an embolectomy performed if it is likely that the acute ischemia is caused by an embolus.[4]

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Case Report:

A 47 yrs old lady, diabetic, normotensive, admitted in cardiac surgery department on 12th September 2013 with diagnosis of chronic rheumatic heart disease, severe mitral stenosis, single vessel coronary artery disease (LAD – 65-75% stenosis in proximal segment), aortic regurgitation (G-II), moderate pulmonary hypertension and atrial fibrillation. She was preparing for double valve replacement and coronary artery bypass graft operation. On 2nd October, 2013 night she reported pain in her both legs and coolness, On examination her pulse was 110 beats/mins, irregular, BP- 80/50 mmHg, both legs were cool from the toes to the knees. Femoral, popliteal and pedal pulses were absent in both legs, sensory and motor function diminished. Subcutaneous heparin started immediately. Duplex study of lower limb arterial system showed absence of blood flow in both external iliac, common femoral artery to downwards. Sudden occlusion of terminal aorta was our diagnosis (Figure-I). She was prepared for embolectomy operation through bi-femoral approach. Next day morning after 16 hours of onset of symptoms, both common femoral artery were exposed through groin incisions under spinal anaesthesia (Figure-II). Control taken on both common femoral artery (CFA), superficial femoral artery (SFA) and deep femoral artery (DFA).

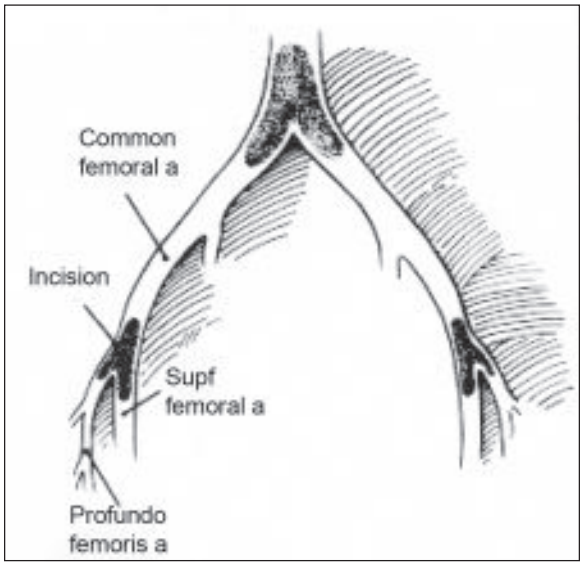

Fig.-1: *Diagrammatic view of distal aorta and its bifurcation. Thrombus at aortic bifurcation with site of incision at common femoral artery.*

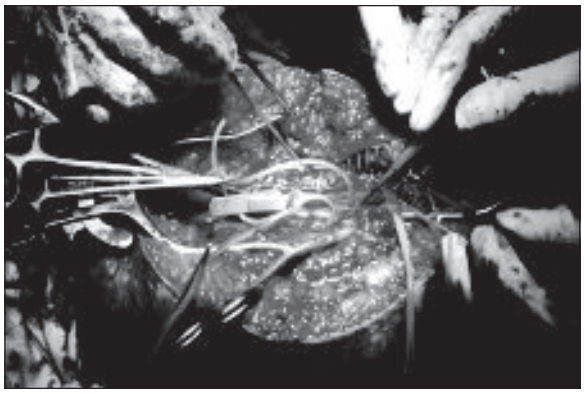

Fig.-2: *Exposure of femoral artery at groin.*

Transverse arteriotomy were made in both common femoral arteries just proximal to bifurcation, Fogarty balloon catheter was passed in a retrograde fashion into the aorta through femoral arteriotomies. Large amount of acute thrombus were removed from both sides (Figure-III). Blood flow was re-established with strong distal pedal

Fig.-3: *Thrombus after removal by embolectomy.*

pulses. Bilateral antegrade embolectomies of the superficial and deep femoral arteries were done. The transverse arteriotomies were closed. Both groins wounds were closed keeping two drain tube in situ. Drain tubes were removed on 2nd post operative day. Lower extremity pain decreased and

sensory and motor activity improved over following week. Stitches were removed on 10th post operative day. She was discharged on the 10th post operative day. After two month she again admitted for valve replacement and coronary artery bypass graft (CABG) operation. Double valve replacement and CABG operation was performed successfully and she was discharged from hospital with advice.

Discussion:

Acute arterial ischemia is caused by emboli or by acute thrombosis superimposed on a chronic underlying partial obstruction. Emboli can be of cardiac or noncardiac origin. 80% of all emboli originated from the heart, the majority of these being of left atrial origin in patients with rheumatic heart disease and atrial fibrillation.[4] Our patient had valvular heart disease and atrial fibrillation.

The clinical picture of acute arterial occlusion includes the classic 6 "P's": pain, paresthesia, paralysis, pallor, pulselessness, and poikilothermia.[1] Our patient presented with all of these symptoms.

Current management options of patients with distal aortic occlusion include anticoagulant therapy, embolectomy or amputation. Heparin alone is not effective in management of arterial ischemia, but may prevent the propagation of a thrombosis.[2] An embolectomy to reestablish blood flow is required unless the patient is moribund or gangrene has already occurred.[3] Prior to the 1960s, a direct transaortic approach was popular.[2] Currently, however, a bilateral transfemoral embolectomy is the procedure of choice for aortoiliac embolic occlusion.[1,2] If blood flow cannot be reestablished, a bypass may be required.[1] In our patient treatment with heparin started immediately. Embolectomy was performed through bi-femoral approach and blood flow was reestablished with strong distal pedal pulses and patient's both limbs were saved.

The Fogarty balloon catheter, introduced in the 1960s, significantly changed aortoiliac emboli management, simplifying and expediting the procedure.[2] A study by Elliot et al comparing the surgical results of 31 pre-Fogarty patients with 62 Fogarty embolectomy patients, founds a 10% decrease in the amputation rate, and a 15% decrease in the mortality rate following the introduction of the Fogarty catheter.[2] In our patient Fogarty embolectomy was successful and patients both limb were saved which support the above study report.

Classical knowledge states that the earlier the embolectomy (especially when it is within the first 8 hours), the better the result. However, cases of successful embolectomies performed a few days after an acute occlusion have also been reported.[3] Olwin in 1953 reported successful embolectomy in four of six patients who presented 22 hours to 3.5 months after embolism.[3] In 1959 Haimovici reported 10 cases of late embolectomy (13 hours to 20 days).[3] In our patient embolectomy was performed 16 hours after onset of acute symptoms, which supports the above study reports.

Conclusion:

A case of saddle embolism at aortic bifurcation is described. Embolectomy performed 16 hours after the onset of symptoms through bi-femoral approach and it was successful and patient's both limbs were saved.

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