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Abbreviations and symbols must be standard and SI units should be used throughout. Whenever possible drugs should be given their approved generic name. Acronyms should be used sparingly. Statistical analysis must explain the methods used. Reference should follow the Vancouver format. In the text they should appear as numbers starting at 1. At the end of the paper they should be listed (double spaced) in numerical order corresponding to the orders of citation in the text. All authors should be quoted for papers with upto six authors, for papers with more than six authors the first six only should be quoted followed by et al.

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Tables should be as few as possible and should present only essential data. Each table should be type-written on separate sheets, have a title or caption with Roman numbers. All photographs, graphs, diagrams should be referred to as figures and should be numbered consecutively in the text in Arabic numericals. The legends for illustrations should be typed on separate sheets. Photographs and photomicrographs should be unmounted glossy prints. Photomicrographs should have internal scale markers, include in the legend the original magnification and the stain used. Line diagrams and graphs should be on separate sheets drawn with black Indian ink on white paper. A photocopy of all illustrations should be submitted.

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PREDICTING FACTORS OF SEVERE ACUTE PANCREATITIS

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Summary:

Fifty eight patients of acute pancreatitis after being released from the hospital were interviewed to assess whether they developed certain complications suggestive of severe acute pancreatitis. Based on the complications the patients were divided into two groups – severe pancreatitis and not severe pancreatitis and their demographic, clinical and biochemical data were compared between groups to find out the predictors of severe acute pancreatitis. Age range was from 17-80yrs with the peak incidence between the 3rd & 4th decades and also from the 5th decades onwards. Male to female ratio was roughly 3:2. We found that jaundice, oliguria and melaena were much higher in the severe pancreatitis group than those in patients of not severe pancreatitis.

However the difference was not significant (P > 0.05). Total count of WBC was higher in the severe pancreatitis group than in the patients with pancreatitis of not severe group (P = 0.057).The eosinophil percentage was significantly lesser in the severe pancreatitis group than in the other groups(p=0.002).USG findings of swollen pancreas and peripancreatic collection showed a significant relationship in the severe pancreatitis group (P < 0.05)

Introduction

Acute pancreatitis is a potentially serious acute abdominal condition. It is usually self-limiting but serious complications may supervene in 25% of cases[1] with an overall mortality rate of 10% [2]. However, there is a wide variation in its severity, ranging from mild and self-limiting to severe life threatening disease.

From mild disease to multiorgan failure and sepsis, acute pancreatitis is a disorder that has numerous causes, an obscure pathogenesis, few effective remedies, and an often unpredictable outcome.

Mortality rates depends on severity. Severity itself depends greatly on whether or not pancreatic necrosis is present. The effectiveness of any treatment is related to an ability to predict severity accurately, but there is no ideal predictive system or biochemical marker, while several new therapeutic strategies show real promise in reducing morbidity and mortality rates, disagreement remains regarding the appropriateness of different methods of predicting severity of disease.

Many studies had been carried out to identify clinical and objective criteria, which can be used to predict the outcome of the disease. These included clinical assessment by experienced clinicians[3], blood tests such as serum calcium,[4] methaemalbumin[5], fibrinogen[6]. and arterial oxygen level[7]. Unfortunately, their discriminatory ability were not satisfactory. Abdominal paracentesis[8] is better at predicting early than late complications of the disease but is invasive and visceral puncture may occur[9].

Nowadays multifactor prognostic scoring system adopted by Ranson et al.[10] and Imrie et al.[11] are generally accepted. They are satisfactory in that the overall sensitivity is 61-100% and specificity is 85-92%[9,10,12] The multiple laboratory criteria has three inherent disadvantages, however: (1) too may factors and values have to be memorised, (2) assessment of severity needs 48 hours or longer to complete, by that time the patients may have already recovered or deteriorated and succumbed, (3) some of the parameters in the scoring system could be influenced by the treatment given during the 48 hours period[13]. As it is important to assess the severity of the disease at the time of admission, better indices based on objective criteria and readily available data on admission are required. By discriminate analysis, Serum urea and plasma glucose at admission were

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identified to be factors with independent significance in predicting severity. If the presence of either factor higher than the cutoff point (urea > 7.4 mmol/1, glucose > 11.0 mmol/1) was considered as an indication of severe disease, then the sensitivity of this method was 75.0%, specificity 80.3%[14]. Assay of C reactive protein is the only easily available blood test in clinical practice that is a proven discriminator of severe and mild disease, at a cut-off level of 150 mg/ml at 48 h after the onset of symptoms[15].

Considerable effort has been devoted recently to identify the factors that influence the severity of pancreatitis in the hope that therapeutic manipulation of those factor might minimize the severity of an attack. Gukovaskaya et. al[16]. address this issue by presenting evidence suggesting that neutrophils, which have been implicated as one of the factors that promote the worsening of pancreatitis, may carry out this function by facilitating the intrapancreatic activation of trypsinogen.

There is evidence that pleural effusion on an early chest radiograph, which is freely available as a routine test on admission, is probably useful in predicting complications and / or a fatal outcome[17].

So far no study has been carried out in Bangladesh to find out predictors of severe acute pancreatitis. Because of poor socioeconomic condition extensive investigations including CT scan can not be done in many cases in the country.

We, therefore, plan to undertake a study on the patients with acute pancreatitis to determine whether a simple and reliable system could be developed to predict the onset of severe acute pancreatitis on the basis of clinical features and available laboratory data on admission.

Aim & Objectives

To identity factors which can predict the possibility of severe acute pancreatitis on the basis of clinical criteria and available laboratory data during the day of admission.

Materials and methods:

This study is a prospecting, purposive, open type of study, which was carried out during the period of June 2005 to April 2006 in Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka, Dhaka Medical College and hospital & Bangladesh institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorderes (BIRDEM), Dhaka.

In this series a total of fifty eight cases of acute pancreatitis was analyzed. Patients of all ages and both sexes were included. The diagnosis of acute pancreatitis was based on the presence of appropriate clinical evidence accompanied by a serum amylase level greater than three times the normal value. Normal value of serum amylase is upto 220 U/L (Boehringer Mannheim GmbH Diagnostica).

Clinical feature consistent with acute pancreatitis with elevated serum amylase level were included in this study.

Patient with a serum amylase level greater than three times the normal value with a diagnosis of pancreatic or periampulary cancer, chronic pancreatitis, perforation of the gut, intestinal obstruction and known diabetic were excluded from the study sample.

For the collection of data a predesigned case collection format was used and patients clinical presentation was recorded and available laboratory variables were used. Sociodemographic characteristics were age, sex, occupation were noted. Among clinical presentation, abdominal pain, vomiting, pulse, systolic and diastolic BP, respiratory rate, cyanosis, jaundice, oliguria, haematemesis and melaena were noted. Among laboratory variables, total count of WBC, DC of WBC, blood urea, serum creatinine, serum SGPT, blood glucose, serum amylase, x-ray chest P/A view, USG of whole abdomen were done.

Reports of haematological, biochemical and imaging tests were documented during the time of hospital admission. After being released from the hospital patients were interviewed to asses whether they developed any complications which is in favour of severe acute pancreatitis.

During the study period, available data at the time of hospitalization were analyzed to find out any predictors of severe acute pancreatitis. Three demographic (age, sex and occupation), eleven clinical (abdominal pain, vomiting, pulse, systolic BP, diastolic BP, respiratory rate, cyanosis, jaundice, oliguria, haematemesis and melaena). Twelve laboratory (Total count of WBC; percentage of neutrophil, lymphocyte, monocyte & eosinophil; blood urea, serum creatinine, serum SGPT, blood glucose, serum amylase, x-ray chest P/A view, USG finding) parameters were obtained within the day of hospitalization.

All patients were followed up after 2 months from the initial attack of acute pancreatitis. Some were followed up over telephone contact & some were followed up by appointment at particular time & date.

The patients were followed up with the help of following investigations:-Total count of WBC, DC of WBC, random blood sugar, serum creatinin, CXR P/A view, ECG, USG of whole abdomen .

GI haemorrhage & cholangitis were diagnosed on the basis of history alone.

Statistical analysis was done by chi-squared test (c^2) Fishers exact-test, students t test, where necessary. Regression analysis was done to see individual predictors by bivariate analysis & independent predictors analysed by multivariate analysis. P values of less than 0.05 ($P<0.05$) were considered to be significant.

Results

A total of fifty eight patients of acute pancreatitis after being released from the hospital were interviewed to assess whether they developed certain complications suggestive of severe acute pancreatitis. Based on the complications the patients were divided into two groups – severe pancreatitis and not severe pancreatitis and their demographic, clinical and biochemical data were compared between groups to find out the predictors of severe acute pancreatitis.

Fig 1. demonstrates 62% of the selected study cases were male and the rest 38% were female with male-female ration of roughly 3:2.

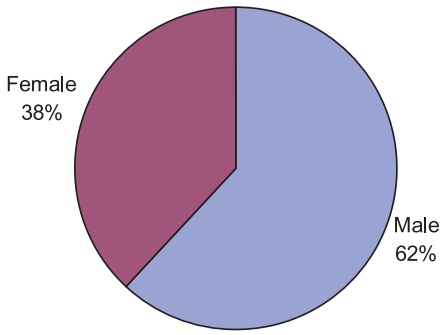

Fig.-1: *Sex distribution of the patients (n=58).*

In terms of occupation approximately one-third (32.8%) patients were housewives followed by 24.1% service-holders, 20.7% businessmen, 3.4 daylabour and another 3.4% were students. The rest 15.5% were engaged with other diverse occupations.

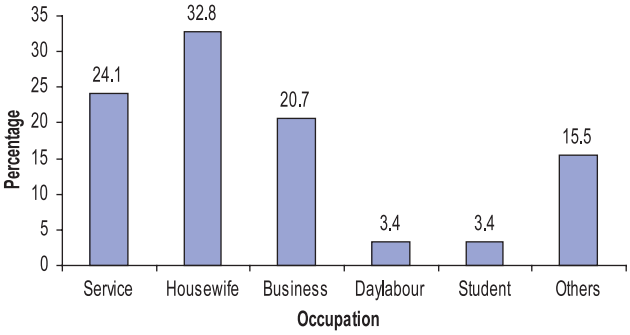

Fig.-2: *Distribution of the patients by occupation.*

Fig. 3 shows the complications encountered by the patients within 2 months after being released from the hospital. More than 20% of the patients developed diabetes mellitus, GI bleeding and pancreatic pseudocyst each 6.9%, pancreatic abscess 5.2%, cholangitis, renal failure and myocardial infarction each 3.4%, pulmonary complication and intraabdominal abscess each 1.7%. Five patients (8.6%)died during the same period of follow up.

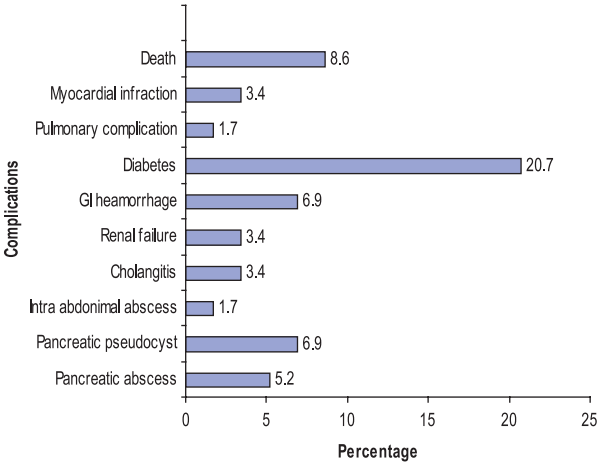

Fig.-3: *Distribution of the patients by follow up after two months.*

Fig. 4 depicts that severe pancreatitis and not severe pancreatitis were equally divided into two groups.

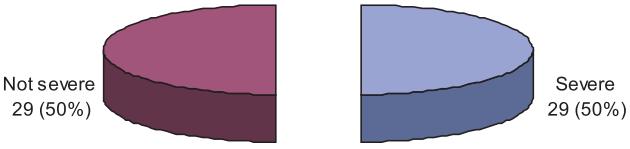

Fig.-4: *Distribution of the patients by severity of pancreatitis (n=58).*

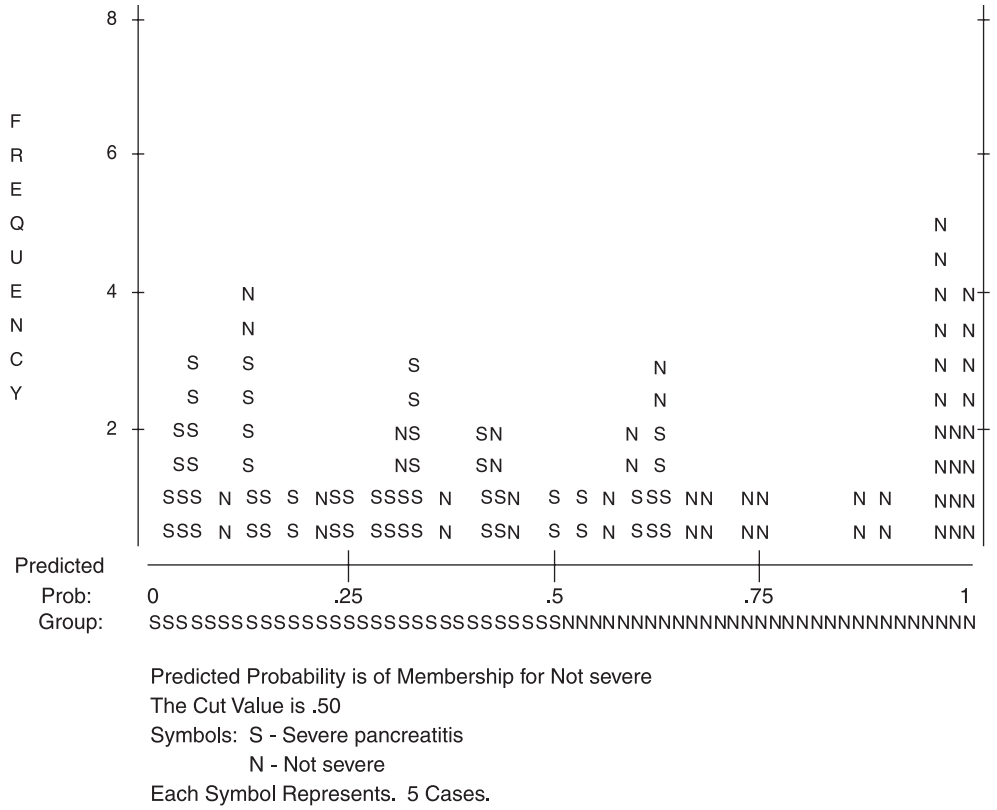

Fig.-5: *Observed Groups and Predicted Probabilities*

Table I shows that out of total 58 patients 21(36.2%) were between the age of 30 – 40 years and another 21(36.2%) were 50 years of age and above. About 14% were between 20 – 30 years, 10.3% between 40 – 50 years and only 3.4% below 20 years of age.

Table II compares the demographic data between severe and not severe pancreatitis. Neither any particular age nor any particular sex was associated with severe pancreatitis, although age 50 years and above and male sex were found to be in higher frequencies in severe pancreatitis group compared to those of not severe pancreatitis group ($p > 0.05$).

Table IV shows that total count of WBC was higher in the severe pancreatitis group than that in the patients with pancreatitis of less severity ($p = 0.057$). The eosinophil percentage was significantly less in the former group than that in the latter group (2.0 ± 0.8 % vs. 4.0 ± 0.6 %, $p = 0.002$).

Table V compares the USG findings of pancreas between the two groups. The incidence of swollen pancreas and peripancreatic collection were observed to be significantly higher in the severe pancreatitis group compared to those in the patients of not severe pancreatitis ($p < 0.05$).

Table-I

Age distribution of the patients (N = 58):

Age (yrs)#	No	%
< 20	02	3.4
20 – 30	08	13.8
30 – 40	21	36.2
40 – 50	06	10.3
e” 50	21	36.2

Median age = (38.0 ± 1.9) years; range = (17 – 80) year.

Table II

Demographic predictors of severe pancreatitis(bivariateanalysis)

Demographic variables	Pancreatitis		p-value
	Severe (n = 29)	Not severe (n = 29)	
Age (³ 50 years)¶	12(41.4)*	9(31.0)	0.412
Sex (male)¶	19(65.5)	17(58.6)	0.588
Occupation (housewife)¶	9(31.0)	10(34.5)	0.780

* Figures in the parentheses denote corresponding %; ¶ Chi-squared Test (c^2) was conducted to compare the distribution of events between groups

Table-III

Clinical predictors of severe pancreatitis (bivariate analysis):

Predictors	Pancreatitis		p-value
	Severe (n = 29)	Not severe (n = 29)	
Vomiting¶	15(51.7)	19(65.5)	0.286
Cyanosis#	1(3.4)	1(3.4)	0.754
Jaundice¶	7(24.1)	3(10.3)	0.164
Oliguria#	7(24.1)	2(6.9)	0.072
Haematemesis#	1(3.4)	1(3.4)	0.754
Malaena#	4(13.8)	1(3.4)	0.176

* Figures in the parentheses denote corresponding %;
¶ Chi-squared Test (c^2) was conducted to compare the distribution of events between groups
# Fisher's Exact Test was done analyse the data; level of significance was 0.05.

Table IV

Association between WBC picture and severe pancreatitis

WBC picture#	Pancreatitis		p-value
	Severe (n = 29)	Not sever (n = 29)	
Total count of WBC (...../ml)	15944 ± 1030	13488 ± 745	0.057
Neutrophil (%)	79 ± 13	74 ± 9	0.133
Lymphocyte (%)	17 ± 11	18 ± 7	0.504
Monocyte (%)	3 ± 1	4 ± 2	0.187
Eosinophil (%)	2.0 ± 0.8	4.0 ± 0.6	0.002

* Figures in the parentheses denote corresponding %;
# Data were analysed using Student's t-Test and presented as mean ± SD.

Table-V

Association between USG findings and severe pancreatitis

USG findings	Pancreatitis		p-value
	Severe(n = 28)	Not severe (n = 29)	
Swollen pancreas¶	22(78.6)*	12(41.4)	0.004
Peripancreatic collection#	7(25.0)	1(3.4)	0.023

* Figures in the parentheses denote corresponding %;
¶ Chi-squared Test (c^2) was conducted to compare the distribution of events between groups
# Fisher's Exact Test was done analyse the data; level of significance was 0.05.

Table-VI

Logistic regression analysis for predictors of severe acute pancreatitis

Predictors	Bivariate analysis Pancreatitis			Multivariate analysis	
				Hosmer and Lemeshow Test (p-value)	Odds Ratio (95% CI)
	Severe (%)	Not severe(%)	p-value		
Oliguria (%)	24.1	6.9	0.072		0.3 (0.44 – 2.86)
Pulse (mean ± SD)	95 ± 12	87 ± 10	0.007		0.9(0.89 -1.02)
Systolic BP (mean ± SD)	127 ± 16	119 ± 10	0.037		0.9(0.92 - 1.02)
TC of WBC (mean ± SD)	15944 ± 1030	13488 ± 745	0.057	0.545	1.0 (1.0- 1.0)
Eosin Phil (mean ± SD)	2.0 ± 0.8	4.0 ± 0.6	0.002		2.0**(1.02- 4.20)
Swollen pancreas (%)	78.6	41.4	0.004		7.1**(1.3 - 37.4)
Peripancreatic collection (%)	25.0	3.4	0.023		0.6(0.03 - 9.97)

** Significant predictors.

Of the 7 variables entered into the model, swollen pancreas demonstrated by USG and decreased eosinophil percentage were found to be the independent predictors of severe acute pancreatitis with ORs being 7.1 (95% CI 1.3 – 37.4) and 2 (95% CI 1.02 – 4.20) respectively.

Discussion

This study was a prospective study on 58 patients of acute pancreatitis. Those patients who were admitted in the BSMMU, DMCH and BIRDEM with features of acute pancreatitis were included in this study. Although-the results of this study cannot be

considered to be representative of all the cases of acute pancreatitis in our country, as no such study has yet been conducted.

Acute pancreatitis is an acute inflammatory process of the pancreas with variable involvement of peripancreatic tissue or remote organ systems. It ranges in severity from a mild self-limited disease to a catastrophic one with multiple severe complications and the risk of death. If we know the predictors of severe acute pancreatitis we can take early measures to prevent complications.

In this study the age range of patients was 17 to 80 years with two peaks- one peak between the 3rd & 4th decades, and the other peak from 5th decade onwards, whereas, the main age group affected in western countries is between 4th to 6th decades. In our country the relative lower age incidence of acute pancreatitis may be due to lower life expectancy of Bangladeshi people.

In this study male to female ratio was roughly 3:2. In industrialized countries acute pancreatitis more commonly affects male than female and this is due to increased alcohol intake by male[19].

After two months of follow-up we found that the incidence of diabetes mellitus is high (20.7%) in the severe pancreatitis group. More than 20% of the patients developed diabetes mellitus; GIT bleeding and pancreatic pseudo cyst like complications occurred in 6.9% each. While pancreatic abscess 5.2%; cholangitis, renal failure and myocardial infarction each 3.4%; pulmonary complications and intraabdominal abscess was 1.7% each. Besides these 8.6% patient died during the same period of follow up.

A major deficiency of the multifactor prognostic scoring system is the large number of factors that are involved. Complete data of each patient are often not available. To assume unmeasured factors as negative would seriously affect the validity of the scoring system. Efforts have been made to reduce the number of significant factors by multivariate analysis.

In 1974 Romero et al[20] identified seven significant variables on admission in predicting severity. Unfortunately five of the seven variables (abdominal pain, distension, as cites, mass and chest roentgenogram findings) were subjective and difficult to quantify. Our study showed that jaundice, oliguria and melaena were much higher in the severe pancreatitis group than in that of patients of not severe group, while the frequency of vomiting was less in the former group than that in the later group. However, the differences did not reach the level of significance ($p>0.05$).

In our study total count of WBC was nearly significantly higher in the severe pancreatitis group than that in the patients without severe pancreatitis ($p=0.057$).

Percentage of eosin Phil was significantly lesser in the former group than that in the later group (2.0±8% vs 4.0±0.6%, $p=0.002$). This feature may help to develop a new predictor for predicting severe pancreatitis.

STFan et al[18] analyzed blood glucose values of the patients with acute pancreatitis on admission. They found that blood glucose level more than 11 mmol/L was associated with severe pancreatitis. In our study development of diabetes mellitus was considered to be an indicator of severe pancreatitis. We found that 20.7% developed diabetes mellitus, which is an indicator of severe pancreatitis.

All patients of this series underwent ultrasonographic examinations. In our study the incidence of swollen pancreas and peripancreatic collection was observed to be significantly higher in the severe pancreatitis group compared to the other group of acute pancreatitis who were not considered to have severe pancreatitis ($p<0.05$).

A possible drawback of our new approach is that the plasma glucose concentration at the time of admission can be influenced by non-pancreatic factor such as rising incidence of glucose intolerance with age.

We followed up the patients mainly over telephone and some patients were followed up by appointment at particular time & date. So in that case patient may not clarify his complication accurately over telephone.

It appears from this study that the low eosinophil percentage and ultrasonographic finding of swollen pancreas at the time of admission were found to be independent predictors of severe acute pancreatitis.

Conclusion

Simple & easily available methods of assessment including low eosinophil percentage & ultrasonographic finding of swollen pancreas on the day of admission may be used to predict the severe attacks of acute pancreatitis.

This may be of immense value in a developing country like Bangladesh, where there are limited financial & technological resources.

However, it is proposed that further study with more detailed recording of relevant data from primary care hospitals, including increasing the number of patients should be carried out for such predictive factors of severe acute pancreatitis.

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DIAGNOSIS AND TREATMENT OUTCOME OF TUBERCULAR CERVICAL LYMPHADENITIS: ANALYSIS OF 61 CASES IN A PRIVATE HOSPITAL OF DHAKA CITY

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Abstract

Sixty-one cases of tubercular cervical lymphadenitis in a private hospital of Dhaka city during the period from January 2005 to August 2007 were studied. Detailed history and thorough physical examination was done for each case. Appropriate investigations especially fine needle aspiration and in selected cases biopsy were done to confirm the diagnosis. Most of the patients were below 50 yrs of age. Service holders, students, businessmen and housewives were the major bulk of the patients. Vast majority of the patients presented with only cervical lymphadenitis, and only few cases presented with axillary and inguinal lymphadenopathy along with cervical. By FNAC, diagnosis of tubercular lymphadenitis was found in 83.60%, but 27.86% required biopsy. Standard short course antitubercular category-I treatment regimen for six months was given for each patient. Some patients require treatment for nine months. Response to antitubercular therapy was evaluated at monthly interval and any adverse reactions of the drugs were noted. With good compliance, response to therapy was satisfactory with only few tolerable adverse reactions that were managed symptomatically without any interruption of therapy.

Introduction

Tuberculosis is the major health problem in Bangladesh [1] and it is a leading cause of mortality and morbidity in human being throughout the world[2]. Prevalence of extra pulmonary tuberculosis is increasing worldwide.[3,4] Tubercular lymphadenitis is the commonest form of extrapulmonary tuberculosis among which tubercular cervical lymphadenitis constitutes the predominant lymph node group involved.[5, 6] Tuberculosis should be strongly considered, even if tuberculin test (MT) is negative.

Lymph node pathology showing characteristic caseation granuloma establishes the diagnosis of tubercular lymphadenitis, even if culture is negative. FNAC is a less cost effective, safe, easy and rapid cytological method for tissue diagnosis. Scandinavian workers developed large-scale use of this technique and other workers had reported 90-98% accuracy rate[7,8]. In the regions like Bangladesh, tuberculosis is endemic. Treatment can be instituted without the need for excisional biopsy, if FNAC show characteristic caseation granuloma.[9]

Management of tuberculosis is difficult in developing countries and was not well organized until a few years back.[10] Difficulties include multiple drugs, cost of drugs, long duration of treatment and poor compliance. So, each and every patient should be instructed properly about the importance of regular intake of antitubercular drug and probable danger of irregularity and noncompliance. This study was designed to see the diagnostic approach including importance of FNAC as well as treatment outcome of tubercular lymphadenitis with standard short course category-1 antitubercular chemotherapy.

Materials and Methods

Sixty-one consecutive new cases of tubercular cervical lymphadenitis were collected from inpatient & outpatient department and consultant's chamber of Green Life Hospital, Dhanmondi, Dhaka from January 2005 to August 2007. Detailed history and thorough

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physical examination was done in every case. Age, sex, occupation, symptoms and signs including fever, cough, expectoration, chest pain, breathlessness, anorexia, weight loss, subcutaneous nodular swelling, sinus, abscess were recorded in a structured questionnaire. Investigations including CBC, hemoglobin (gm/dl), erythrocyte sedimentation rate (ESR) chest X-ray P/A view, tuberculin test, sputum for AFB, fasting blood glucose, FNAC and in selected cases, biopsy from cervical lymph node with or without excision and USG of whole abdomen were done. Liver and renal function tests were done, when required. FNAC reports showing characteristic caseation granuloma suggestive of tubercular lymphadenitis was considered as confirmed diagnosis of tubercular cervical lymphadenitis and enrolled in the study protocol.

Defaulter, relapse and treatment failure cases of tubercular lymphadenitis were excluded from the study.

Definition of terms

1. New cases of tubercular lymphadenitis: A new case of tubercular lymphadenitis is defined as "a patient of tubercular lymphadenitis who has never received antitubercular drugs or received antitubercular drugs for less than one month".
2. Defaulter case of tubercular lymphadenitis: A defaulter case is defined as "a patient of tubercular lymphadenitis who previously completed at least one month of antitubercular treatment and returned after at least two months of interruption of treatment".
3. Relapse case of tubercular lymphadenitis: A relapse case is defined as "a patient of tubercular lymphadenitis who previously completed antitubercular treatment and was cured but has again developed either symptoms or signs of tubercular lymphadenitis".

The standard short course category-1 antitubercular treatment regimen (2HREZ/4HR) for six months was given to each and every patient with appropriate dose adjustment according to the body weight. Response to antitubercular therapy was evaluated at monthly interval and any adverse reactions of the drugs were noted. Data were compiled and analyzed with computer-based programme.

Results

A total of 61 patients were enrolled and analyzed after completion of treatment. Age range is 16 to 58 years with a mean age of 31±8 years. Out of 61 patients 35 were male and 26 were female with a male-female ratio of 3.5:2.6. Age, sex and occupation of the patients are shown in table-I. Majority of the patients were from lower and middle income groups. Clinical variables of patients were shown in table-II. Out of 61 patients, fever (75.40%), loss of appetite (77.04%) and weight loss in (67.21%) were found.

Table-I

Demographic variables (n=61)

Variables	Number (Percentage)
Age (years)	
<19	8 (13.11%)
20-29	17 (27.86%)
30-39	20 (32.79%)
40-49	9 (14.75%)
50-59	5 (8.20%)
e"60	2 (3.27%)
Sex	
Male	35 (57.37%)
Female	26 (42.62%)
Occupation	
Service holder	16 (26.22%)
Business man	13 (21.31%)
Student	12 (19.67%)
Housewife	10 (16.40%)
Cultivators	7 (11.47%)
Others	3 (4.91%)

Vast majority of patients presented with only tubercular cervical lymphadenitis. As shown in table-II, multiple lymph nodes were present in 77.04% cases with matted lymph node in 52.46%. Lymph nodes were nontender in 78.68% of the cases with firm consistency in 83.60%. 11.47% cases had abscess and 4.91% cases had sinus. The duration of symptoms were from 4 weeks to one year with mean of 5± 2 months.

Table-III. shows baseline investigation findings. Leucocytosis with neutrophilia in 36.06%, ESR more than 30mm in 1st hour in 67.21%, tuberculin test was positive in 77.04%. Patchy opacity suggestive of pulmonary tuberculosis was present in 11.47% and sputum smear positive in 4.91% of cases. FNAC showed granuloma suggestive of tubercular lymphadenitis in 83.60 % of patients. Biopsy required in 27.40% for the diagnosis.

Table-II

Clinical variables (n =61)

Variables	Number (Percentage)
Clinical characteristics	
Subcutaneous nodules	61 (100%)
Fever	46 (75.40%)
Loss of appetite	47 (77.04%)
Loss of weight	41 (67.21%)
Cough	18 (29.50%)
Expectoration	5 (8.19%)
Hemoptysis	2 (3.27%)
Areas of lymph node involvement	
Cervical	47 (77.04%)
Cervical & axillary	9 (14.75%)
Cervical, axillary & inguinal	5 (8.19%)
Characteristics of lymph node	
Single	14 (22.95%)
Multiple	47 (77.04%)
Discrete	15 (24.60%)
Matted	32 (52.46%)
Firm	51 (83.60%)
Soft	10 (16.40%)
Non-tender	48 (78.68%)
Tender	13 (21.31%)
Fixity to overlying skin & underlying structures	5 (8.19%)
Abscess	7 (11.47%)
Discharging sinus	3 (4.91%)

Management outcome of the patients after six months of antitubercular treatment is shown in table IV, where it is seen that 83.60% of the patients had been clinically cured, 6.55 % were clinically cured with extended treatment (nine month), 4.91% of patients were clinically cured with surgical excision, 3.27 % did not respond to treatment and 1.63 % dropped out. Patients who were detected and treated early had early and rapid response to therapy. Total disappearance of symptoms and signs including disappearance of subcutaneous lymph node swelling were noted during follow up visit at monthly interval. Pruritus (13.11%), maculopopular skin eruption (8.20%), nausea (11.47%), vomiting (4.91%), and arthralgia (3.27%), were the adverse effects of drugs.

Table-III

Baseline investigations findings of the patients (n=61)

Investigations	Number (Percentage)
Total count of WBC <11000/cu.mm	44 (72.13%)
Total count of WBC >11000/cu.mm	17 (27.86%)
Differential count of neutrophil< 75%	39 (63.93%)
Differential count of neutrophil> 75%	22 (36.06%)
ESR < 30 mm in the 1st hour	20 (32.78%)
ESR > 30 mm in the 1st hour	41 (67.21%)
MT< 10 mm after 72 hours	14 (22.95%)
MT> 10 mm after 72 hours	47 (77.04%)
X-ray chest PA view with patchy opacity	7 (11.47%)
Sputum smear AFB positive	5 (4.91%)
Lymph node FNAC suggestive of tuberculosis	51 (83.60%)
Lymph node biopsy suggestive of tuberculosis	17 (27.86%)

Table-IV

Treatment outcome of the patients (n=61)

Treatment outcome	Number (Percentage)
Clinically cured	51 (83.60%)
Clinically cured with extended treatment (nine month)	4 (6.55%)
Clinically cured with surgical excision	3 (4.91%)
Not cured	2 (3.27%)
Dropped out	1 (1.63%)

Discussion

In this study, majority of the patients were between 16 and 50 years of age. Most of the patients were in their active years of life. The world health organization reported highest incidence of tuberculosis in this age group.[2] Almost similar observations were found in another study.[12] In our study, male to female ratio was 3.5:2.6. In one study, male to female ratio was noted as 3.1:1.9 and in another study, male to female ratio was 2.1:1.2, which is closely similar to the present series.[13]Majority of the patients in our study were service holders (26.22%), student (21.31%) and businessmen (19.67%). In one study, businessmen and students were 18.90% and 14.90% respectively.[14] In another study affected students were 17.50%.[15] These observations are closely similar to that of present series.

Fever, loss of appetite and loss of body weight are common, but not invariable features of tubercular lymphadenitis. Of course, patients may present otherwise asymptomatically with visible or palpable lump, which may remain undetected for several months due to painless and very slow enlargement of lymph nodes. In our series, 68.38% of the patients had fever, loss of appetite and body weight. Fever was recorded in 70% of the patients in another series[15], which is very closely similar to our series.

In the present series, 77.04% of the patients presented with only tuberculous cervical lymphadenitis, but axillary and inguinal regions were involved in only 14.71% and 8.19% of the cases respectively. In one series 86.29% of the cases presented with tuberculous cervical lymphadenitis, whereas axillary and inguinal lymph nodes were involved in 10.35% and 3.45% of the cases respectively.[15] These findings were just similar to that of the present series. Similarly, in another series tuberculous cervical lymphadenitis (72%) was predominant, followed by axillary (24%) and inguinal (2%) regions.[16] All these observations indicate that tuberculous cervical lymphadenitis is the commonest from of tubercular lymphadenitis.

Tubercular lymphadenitis may present as a unilateral single or multiple or bilateral multiple painless lump, mostly located in the posterior cervical or supraclavicular region.[17] In our series, most of the patients presented with multiple (77.04%), firm (83.60%), matted (52.46%), and nontender (78.68%) lymph nodes free from overlying skin and underlying structures and mostly located in the posterior cervical and supraclavicular regions.

FNAC is a satisfactory tool in the diagnosis of tubercular lymphadenitis. The procedure is simple, safe, repeatable, and inexpensive and can be recommended on an outpatient basis. However, histopathological examination is required for definitive confirmation in patients of reactive hyperplasia and chronic nonspecific lymphadenitis diagnosed by FNAC.[18] In the present series, FNAC showed caseation granuloma suggestive of tubercular lymphadenitis was found in 83.60% cases. The rest 27.86% of the cases required excisional biopsy for confirmation of diagnosis, as because in these cases FNAC reports were given either as reactive hyperplasia or chronic nonspecific lymphadenitis. In some other series, it has been shown that FNAC detected tubercular lymphadenitis in 25 to 77% of the cases.[19] The sensitivity and specificity of FNAC in the diagnosis of tubercular lymphadenitis are 88% and 96% respectively.[20] Combination of FNAC with culture or Mantoux test further increases the diagnosis yield in tubercular lymphadenitis.[21] In our series, culture of FNAC specimen was not done, but Mantoux test was positive in 77.04%. In another series, Mantoux test was found positive in 60% of the cases. FNAC is a sensitive, specific, and cost effective way to diagnose tubercular lymphadenitis.[20]

Patients with subacute and chronic lymphadenitis especially from Indian subcontinent, where the disease is endemic, tuberculosis should be strongly considered even if Mantoux test is negative and sputum smear is negative for AFB. Lymph node FNAC showing caseation granuloma establishes the diagnosis, even if the culture is negative.[16]

There are treatment schedules of six and nine months duration, which have similar relapse rates of 3.3%and 2.7% respectively. [22] Six months treatment is adequate in most patients, but some authors advocate 12 month therapy for tubercular lymphadenitis, which results in complete cure after two years of follow up in nearly all cases.[17,23] A tubercular lymphadenitis usually responds very well to antituberculous chemotherapy.[24] Surgery has a limited role in the treatment. A surgical intervention in tubercular lymphadenitis should include fine needle aspiration, drainage, and incisional or limited excisional biopsy.[25]

Conclusion

Tubercular cervical lymphadenitis is the most common form of extra pulmonary tuberculosis. FNAC is a fairly reliable diagnostic procedure for the diagnosis of tubercular lymphadenitis. It can enable us to avoid hazardous, costly and time-consuming unnecessary surgery for biopsy. After history taking with physical examination and investigations like ESR and MT, diagnosis of tubercular cervical lymphadenitis can be confirmed by FNAC. The outcome of treatment of tubercular cervical lymphadenitis with standard short course category-1 antitubercular treatment regimen for six months is satisfactory.

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RESPONSE WITH PEGINTERFERON A-2A AND RIBAVIRIN IN CHRONIC HEPATITIS C

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Summary:

Peginterferon a-2a with ribavirin produces significantly higher sustained virological response in comparison to conventional interferon monotherapy in patients with chronic hepatitis C virus (HCV) infection. We evaluated the efficacy and safety of peginterferon a-2a plus ribavirin combination in the treatment of chronic hepatitis C among Bangladeshi patients. This prospective study was conducted in the department of Gastroenterology. The period of study was from July 2004 to July 2006.

A total 26 patients were randomly selected in this study and were assigned to treatment who received peginterferon a-2a 180 mg once weekly plus ribavirin (800 or 1000 mg - 1200 according to body weight) daily for 24-48 weeks depending on genotypes. Efficacy was assessed by measurements of serum HCV-RNA and serum aminotransferase.

A higher proportion of patients (76.92%) who received peginterferon

a-2a plus ribavirin had a sustained virological response. It is observed that genotype 3(a and b) patients showed poor response (ETR-57.14%), where as genotypes 1(a, b), 3 and 4 mixed, 2b and 4 infections showed response rate of 100%. So it can be concluded that once weekly peginterferon a-2a plus daily ribavirin is effective in chronic HCV infection in Bangladesh and overall response rate is similar to that reported in other studies.

Introduction:

Hepatitis C virus is a major causative agent for chronic liver disease[1,2]. The infection with HCV tends to persist in majority of infected individuals and perhaps as many as 70-90% of the infected individuals fail to clear the virus once acquired. The infection has a significant role in causing chronic hepatitis, cirrhosis and hepatocellular carcinoma[3,4]. The goal of treatment is to prevent complications of HCV infection.

Until recently, when the combination of standard interferon-a plus ribavirin therapy became available, the standard of care in the united states for the treatment of chronic HCV infection was standard interferon-a at a dosage of 3 MIU three times weekly for 12 months[5,6]. Pegylation of interferon-a has created sustained levels of interferon such that only one dose per week would be required. Combination therapy with ribavirin plus pegylated interferon is the most effective regimen currently licensed, having been shown to be significantly superior to standard interferon-a alone in the treatment of patients with chronic HCV infection[7-12].

A number of factors have been shown to be predictive of a favorable sustained response, including viral genotype other than 1, low serum HCV RNA level, absence of cirrhosis, younger age, female gender and shorter duration of infection. Response rates are lower in genotype1[13,14]. Hepatitis C viremia is important as a predictor of response to treatment as well as for monitoring its therapeutic efficacy[15]. Serum of the patient on treatment is tested for HCV RNA at different intervals after treatment, to monitor response to therapy. Suppression of viremia below detectable limits indicates favorable response.

Peginterferon and ribavirin is being used to treat patient with chronic hepatitis due to HCV infection in Bangladesh. Response rate to this therapy is not yet evaluated in any well designed study in Bangladesh. There is a need to determine the response rate in our setting. This study was planned to evaluate the end of treatment response in patients who had taken peginterferon and ribavirin combination therapy for 24-48 weeks and to evaluate sustained virological response after 24 weeks of end of therapy by testing HCV RNA.

Currently there is no vaccine and no effective post-exposure prophylaxis against this dreadful infection. Several treatment options for chronic hepatitis C

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carriers are now available worldwide. However, the benefit in terms of economy (treatment cost plus laboratory charges) and efficacy of treatment differs in different regimens and different regions[14,16-20]. This study is therefore aimed to asses the efficacy and safety of peginterferon a-2a and ribavirin in the treatment of chronic hepatitis C in Bangladesh.

This study was conducted-

- To evaluate the virological response to treatment with peginterferon a-2a and ribavirin in patients with chronic hepatitis C.
- To study the adverse effects of peginterferon a-2a and ribavirin combination therapy.
- To see the response rate with peginterferon a-2a and ribavirin combination therapy according to genotypes.

Materials and methods

This study was a prospective, randomized, open labeled, clinical trial. The period of study was from July 2004 to July 2006 and place of study was department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka.

The patients of chronic hepatitis due to HCV infection were included in this study for treatment with peginterferon a-2a and ribavirin. Therapy was given for 24 weeks in genotypes 2 and 3 infection and for 48 weeks in genotypes 1 and 4 infections as recommended by the American Association for the Study of Liver Diseases (AASLD) on the basis of multicenter study. The patients were planned for follow up to evaluate the end of treatment response (ETR) and sustained virological response (SVR) as well as to monitor side effects of peginterferon a-2a and ribavirin during therapy and upto 24 weeks after completion of therapy.

The patients were recruited from the medical outpatient department of Bangabandhu Sheikh Mujib Medical University Hospital and also from the gastro-hepatology specialists' consultation center in Dhaka.

Selection criteria

Inclusion criteria:

- Male and female patients ³18 year of age
- Serologic evidence of chronic hepatitis C infection by an anti-HCV antibody test for more than 6 months.
- Detectable serum HCV-RNA (Qualitative or quantitative)
- Elevated serum ALT activity
- Compensated liver disease (Child-Pugh Grade A clinical classification)

Exclusion criteria:

- Women with ongoing pregnancy or breast feeding
- Therapy with any systemic anti-neoplastic or immunomodulatory treatment £6 months prior to the first dose of study drug.
- Any investigational drug £6 weeks prior the first dose of study drug
- Co-infection with active hepatitis A, hepatitis B and/or human immnodeficiency virus (HIV)
- History or other evidence of a medical condition associated with chronic liver disease other than HCV (e.g., hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, toxin exposures)
- Signs and symptoms of hepatocellular carcinoma
- History of bleeding from esophageal varices or other evidence of decompensated liver disease.
- Neutrophil count <1500 cells/mm^3 or platelet <100000 cells/mm^3 at screening.
- Serum creatinine level >1.5 times the upper limit of normal at screening
- History of severe psychiatric disease as defined by history of treatment with an antidepressant medication or a major tranquilizer at therapeutic doses for major depression or psychosis, respectively, for at least 3 months at any previous time or any history of the following: a suicidal attempt, hospitalization for psychiatric disease, or a period of disability due to a psychiatric disease.
- History of a severe seizure disorder or current anticonvulsant use.
- History of immunologically mediated disease, chronic pulmonary disease associated with functional limitation, severe cardiac disease, major organ transplantation or other evidence of severe illness, malignancy or any other conditions

which would make the patient unsuitable for the study.

- History of thyroid disease poorly controlled on prescribed medications, elevated thyroid stimulating hormone (TSH) concentrations and any clinical manifestations of thyroid disease.
- Evidence of severe retinopathy (e.g. CMV retinitis macula degeneration).
- Evidence of drug abuse (including excessive alcohol consumption) within one year of study entry.
- Inability of unwillingness to provide informed consent or abide by the requirements of the study.

Twenty-six patients were selected for this study. Out of 26, sixteen patients had genotypes 2 and 3 infections and treatment was continued for 24 weeks. Ten patients had genotypes 1, 4 and mixed (3 and 4) infections and treatment was continued for 48 weeks. Peginterferon a-2a (Inj. Pegasys, Roche Bangladesh Limited) was given at a dose of 180 mgm subcutaneously per week and ribavirin (Cap. Rivarin-200 mg, Roche Bangladesh Limited) was given at a dose of 800 mg for genotypes 2 and 3 infections and 1000-1200 mg for 1 and 4 infections according to body weight daily.

End of treatment response (ETR) was seen at 24 weeks (in case of genotypes 2 and 3 infections) and 48 weeks (in case of genotype 1 and 4 infections). Sustained virological response (SVR) was seen after 24 weeks of end of therapy. ETR and SVR were seen by testing serum for HCV-RNA using PCR method.

Dose-modification guidelines had been established to manage serious haematologic adverse events associated with peginterferon alpha-2a and ribavirin therapy before they can develop into life-threatening situations. The dose of ribavirin was reduced by one half if Hb concentration decreased to <10 g/dl at any time. Furthermore, patients were discontinued from treatment if their Hb was <8.5 g/dL at any time. The dose of peginterferon alpha-2a was reduced to 135 mgm if WBC count was $<1.5\times10^9$ /L, neutrophil count was $<0.75\times10^9$ /L, or platelet count was $<50\times10^9$ cells/L. Combination therapy was permanently discontinued if the WBC count was $<1.0\times10^9$ /L, neutrophil count was $<0.5\times10^9$ /L, or platelet count was $<25\times10^9$ cells/L.

Results

Twenty-six patients fulfilled the inclusion criteria and were treated from July 2004 until July 2006. Six patients (23%) had history of blood transfusion and one patient had history of intravenous drug abuse. Substantial number of patients did not give any history of exposure to risk factors (Table-I).

Table-I

Shows base line characteristics of the patients

Characteristics	Number (%)
Age-year	39±12
Sex-M/F	18/8
Occupation - no. (%)	
Business	12(46)
Housewife	8(30)
Service	6(23)
Marital status- no. (%)	
Married	25(96)
Unmarried	1(4)
Education - no. (%)	
Under graduate	0(0)
Graduate	26(100)
Body weight- Kg	60±4
Risk factors No. (%)	
Transfusion	6(23)
IV drug abuse	1(3)
Unknown	19(73)
Previous history of jaundice - no. (%)	
Yes	8(30)
No	16(61)
Diabetes mellitus - no. (%)	
Yes	4(15)
No	22(84)

Most of the patients (84%) presented with weakness and fatigue (Table-II). Transaminases were elevated in all the patients. Serum albumin and prothrombin time were within normal limit (Table-III).

Table-II

Shows clinical presentation of the patients

Characteristics	Number (%)
Weakness/fatigue	22(84)
Anorexia	18(69)
Nausea	6(23)
Vomiting	1(3)
Abdominal pain	5(19)
Weight loss	4(15)
Burning sensation of the body	6(23)
Sleep disturbance	6(23)
Bodyache	8(30)

Table-III

Shows base-line laboratory parameters

Characteristics	Value
Hb-gm/dl	13.9±0.2
Total count per cmm	6291±730
Platelet count per cmm	212846±6355
Serum bilirubin (mmol/L)	11.8±1.2
Serum ALT (U/L)	118±12.0
Serum AST (U/L)	90.1±10.3
Serum albumin (gm/L)	44.1±1.1
Serum creatinine (mmol/L)	89.7±5.0
Serum TSH (mmol/L)	1.4±0.2
Proth. Time (PTp)	Control-12, Patient-14±2

Most of the patients (92.30%) developed fever after first injection and fatigue. Seventy seven percent patients developed anorexia and 69% developed myalgia and insomnia. About half of the patients (46%) complained of nausea and headache at some time (Table-IV).

Table-IV

Shows frequency of adverse events

Adverse events	Number (%)
Fever after first injection	24(92.30)
Fever during treatment	16(61.53)
Fatigue	24(92.30)
Headache	12(46.15)
Weight loss	8(30.76)
Arthralgia	5(19.23)
Myalgia	18(69.23)
Decreased appetite	20(76.92)
Nausea	12(46.15)
Alteration of bowel habit	2(7.69)
Vomiting	2(7.69)
Abdominal pain	5(19.23)
Depression	3(11.53)
Insomnia	18(69.23)
Cough	5(19.23)
Chest pain	2(7.69)
Alopecia	2(7.69)
Rash	1(3.84)
Hypothyroidism	1(3.84)
Burning eye	2(7.69)

Dose modification was needed for 10 patients. Of these, 8 patients who developed anaemia received ribavirin at a lower dose of 600 mg daily for few weeks. In 2 patients, ribavirin was discontinued for few weeks and the patients were treated with human recombinant erythropoietin (Inj. Recormon 500 IU, subcutaneously 3 times weekly) until anaemia corrected. Six patients who had leucopenia, received peginterferon at 90 mgm weekly for few weeks. Peginterferon was reintroduced at full dose after regaining the normal count. Eight patients developed thrombocytopenia and was treated with 4 units of platelet transfusion along with reduction of dose of peginterferon to half for only 4 weeks. Thereafter full dose was reintroduced. One patient with marked leucopenia and thrombocytopenia peginterferon and ribavirin was stopped for 2 weeks (Table-V).

Table-V

Shows frequency of adverse events

Adverse events	Number (%)
Anaemia	10(38.46)
Leucopenia	6(23.07)
Thrombocytopenia	8(30.76)

Fourteen patients were of genotype 3(a and b), 4 were genotype 1 (a, b), 4 patients were of genotype 3 and 4 mixed and 4 had 2b and type 4 infections, two in each group (Table-VI).

Table-VI

Shows prevalence of genotypes among the patients

Genotypes	Number of patient
3 (a, b)	14
1 (a, b)	4
3 and 4 mixed	4
2b	2
4	2
Total	26

Out of 26 patients tested for end of treatment response (ETR), 20(76.92%) had no detectable HCV RNA and were responders. They also have sustained virological response (SVR) after 24 weeks of end of therapy. The 6 patients of genotype 3(a and b) had no virological response (Figure-1).

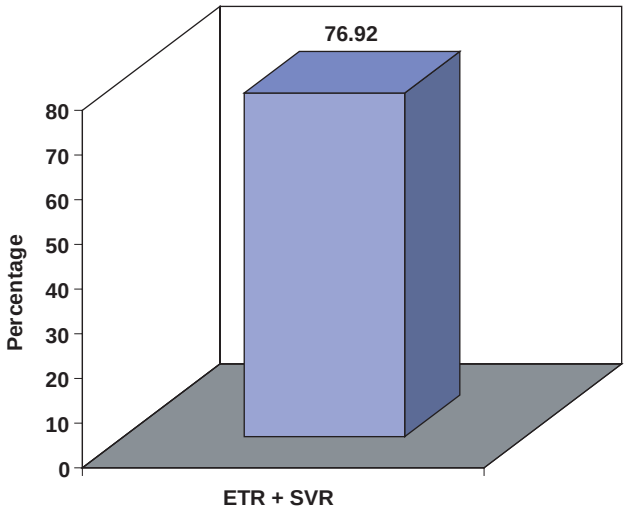

Fig.-1: *Shows end of treatment response (ETR) and sustained virological response (SVR)*

It is found that all the patients of genotype 1(a, b) 3 and 4 mixed, genotype 2b and 4 infection had both ETR and SVR (100%). Out of 14 patients of genotypes 3(a, b) infection tested for ETR and SVR, 8 were responder (57.14%) [Table-VII].

Table-VII

Shows virological response according to genotypes

Genotypes	Number	Responder	Non-responder
3(a, b)	14	8 (57.14%)	6
1 (a, b)	4	4 (100%)	0
3 and 4 mixed	4	4 (100%)	0
2b	2	2 (100%)	0
4	2	2 (100%)	0
Total	26	20(76.92%)	6(23.08%)

Discussion

Infection with hepatitis C virus is a leading cause of liver disease worldwide[1,2]. Progression to chronic hepatitis C occurs in most people acutely infected with HCV and persistent infection is an important cause of cirrhosis, end stage liver disease and hepatocellular carcinoma. Thus, early detection and treatment is of great importance. The goal of treatment is to prevent complications of HCV infection[3,4].

There have been substantial improvements in the success of HCV treatment and there are currently several treatment regimens approved by the FDA. In randomized clinical trials, the highest overall SVR rates have been achieved with the combination of weekly subcutaneous injection of long acting peginterferon a-2a and daily oral ribavirin, which represents the current standard of care[13].

In this study, overall end of treatment response and sustained virological response (SVR) was 76.92%. End of treatment response was slightly better in females. Sustained virological response is higher in genotype 2 and 3 in most of the previous studies[13,14]. In our study genotype 3(a and b) had poor response (57.14%) in comparison with other studies who reported response rate of 76 to 82%[13]. This poor response could be due to selection bias or this may be due to the fact that genotype 3(a and b) patients of Bangladesh are poor responders. On the other hand, while response rate of genotype 1 are reported to be 42 to 46%[13], we got response rate of 100% in our study. As the sample size was very small, it is difficult to comment regarding the cause of this favourable response. The response rate of mixed (3 and 4) infection was also very satisfactory (100%). To ascertain the response rate of various genotypes of HCV infection in Bangladesh, a well designed study incorporating large number of patients of different genotypes is required.

There are several limitations of the study. Number of patients were small. Although serum aminotransferse level was seen in all the patients and found to be normalised after therapy, liver biopsy was not done. So the histological improvement could not be seen.

Although the cost of the treatment is high, this therapy is recommended in those patients who can afford.

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EFFECT OF L-THYROXINE ON SERUM LIPOPROTEINS ABNORMALITIES IN HYPOTHYROID PATIENTS

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Abstract

This study was carried out in the department of Medicine, BSMMU to study the lipoproteins abnormalities in hypothyroid patients and to find out the effects of L-thyroxine therapy in the lipoproteins abnormalities. After thorough examination, and relevant investigations, 80 (eighty) hypothyroid patients and 30 (thirty) healthy euthyroid controls were taken in this study. The selected patients were given L-thyroxine replacement therapy at a dose of 100-200 mg/d. All patients were followed up after 06 weeks of full dose of L-thyroxine therapy and 03 months after achievement of euthyroid state. (M±SD) of total cholesterol (TC), LDL cholesterol (LDL-C) & triglyceride (TG) of patient group (before treatment) were 231.6±62.9 mg/dl, 152.4±59.4 mg/dl & 186.9±95.3 mg/dl respectively. On the other hand (M±SD) of TC, LDL-C & TG of control group were 146.9±23.6 mg/dl, 70.6±25.6 mg/dl & 100.5±39.2 mg/dl respectively. (M±SD) of HDL-C of the patient group and control group was 41.4±3.8 mg/dl & 56.3±11.5 mg/dl respectively. TC (p=0.000), LDL-C (p=0.000), TG (p=0.000) were significantly higher but HDL-C (p=0.000) was significantly lower in the patient group compared to control group. After treatment with L-thyroxine therapy there was significant reduction in TC (p=0.000) and LDL-C (p=0.000), but TG (p=0.057) and HDL-C (p=0.217) did not changed significantly. Hypothyroid patients have lipoproteins abnormalities in the form of high TC, LDL-C, TG & low HDL-C and therapy with L-thyroxine significantly reduces TG & LDL-C but has no significant effect on TG & HDL-C.

Introduction

Hypothyroidism is a common endocrine disorder. Hypothyroidism is associated with many biochemical abnormalities including lipids. Serum TSH levels were related to the levels of LDL and HDL[1]. The prevalence of elevated TSH in hypercholesterolemic patients amounts to 12-13%, whereas in normal population 2.2%[2]. In study from the Mayo clinic, the lipid profiles of 268 consequtive patients with overt hypothyroidism were reviewed and it was found that 91.4% of these patients had abnormal lipid values.[3] So hypothyroidism is a major cause of secondary dyslipidemia[3,4], the cause of which resides in a decrease of cholesterol excretion and in a marked increase in apoB-lipoproteins because of decreased catabolism and turnover by a reduced number of LDL-receptors on the liver cell surface[5]. Dyslipidaemia is a major risk factor for coronary artery diseases. Our aim of this study was to find out the lipid abnormalities, as well as the effect of L-thyroxine in our hypothyroid dyslipidaemic patients.

Subjects and Methods

The study was carried out in the Department of Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka during the period of July 2003 to June 2005. The patients were selected from the Endocrine Out Patient Department of BSMMU. Investigations were done in the Biochemistry Department, BSMMU.It comprised an observational study for estimation of the prevalence of dyslipidemias in hypothyroid patients followed by an open-label uncontrolled clincial trial to assess the effects of L-thyroxine on the dyslipidemia.The clinical course of the disease was explained with each patient in details and they were enrolled after obtaining informed written consent. Permission of the study and ethical clearance was taken from the concerned department prior to the study.

Subjects

The patients who presented with signs and symptoms of hypothyroidism were initially considered for inclusion in the study. After thorough examination, and relevant investigations, the patients who fulfilled the inclusion criteria were initially selected for the study. The diagnosis of hypothyroidism was based on clinical findings and low serum FT_4 and high serum TSH concentration. Diagnosis of hypothyroidism was confirmed by the author, supervisor or co-supervisors.

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Author myself was responsible for treatment and follow-up of the cases.The subjects who seemed healthy were taken as control subjects. None of control subject was diabetic and had clinical or biochemical evidence of thyroid, liver and renal diseases. Conditions known to alter TSH secretion and/or interfere with lipoprotein metabolism were excluded from the study. The particulars of each patients, detailed history and physical examination were noted in the collection sheet.The selected patients were given L-thyroxine replacement therapy gradually before breakfast in a single dose starting with 50mg/day and increasing the dose to 100mg/day at two weeks interval[6,7,8,9]. Then the patients were clinically evaluated (e.g general welbeing, weight reduction, periorbital swelling) after one month. The patients who clinically did not improve, were advised to increase the dose of thyroxine from 100 to150 mg/day; while who were clinically improved, advised to continue the previous dose. After 06 weeks of full dose of L-thyroxine therapy all patients were again followed up clinically and FT4 & TSH were done to assess thyroid status. Euthyroidism was diagnosed on the basis of clinical improvement and normal serum FT_4 and serum TSH concentration. After acheivement of euthyroid state, all patients were finally followed up after three months[10,11,12]. In final follow-up FT4, TSH and lipid profile were estimated after 12-14 hours overnight fasting to see thyroid status and as well as lipid abnormalities. Clinical improvement and biochemical paradmeters were noted in the follow-up sheet during follow-up.Initial and final measurements were performed by the same methods. Thyroid function tests, lipid profile,renal function test, liver function test & fasting blood sugar measurement were done in each patient and control before enrolment at initial visit.

Data Analysis

All data were analyzed with the help of SPSS software programe (version-10.0) and expressed as Mean ± SD. Paired T-test was done to see the significance of lipid profile between before & after treatment of hypothyroid patients. Pearson correlation co-efficient test was done to see the correlation of lipid profile with the severity of hypothyroidism. 'P' values <0.05 were considered significant.

Results and Observations

During the period from July 2003 to June 2005, 80 hypothyroid patients and 30 unmatched healthy controls included in the study. During the study period 18 (eighteen) patients dropped out in the first follow-up and 7 (seven) patients dropped out in the final follow-up. During replacement therapy of L-thyroxine, 65 patients were given LT_4 100 mg/d and 15 patients 150 mg/d on the basis of clinical improvement. Except two all patients became euthyroid after 06 weeks of full dose of L-thyroxine therapy. These two patients were given L-thyroxine at dose of 200 mg/d. Analysis was done with 55 patients and 30 controls.

Age of the patients ranged from 20-60 years. Peak age of the subjects at presentation was observed at 3rd and 4th decade. In the patient group the mean age (M±SD) was 34.4±11.2 years and in the control group was 37.7±5.7 years respectively. Female to male ratio was about 5 : 1 in patient group and 1:1 in control group (Table-1).

Table-I

Study subjects by age & sex

Parameters		Study Subjects	
		Patient group (N=55)	Control group (N=30)
Age in years (Mean±SD)		34.4±11.2	37.7±5.7
Sex	Male	9	15
	Female	46	15
Total	55	30	

TSH (M±SD) of patient group at presentation was 60.0±31.7 miu/L and control group was 1.6±1.4miu/L. TSH (M±SD) of the patient group was much higher than control group. FT_4 (M±SD) of patient group was 5.4±2.9poml/L (Table-2).

Table-II

TSH and FT_4 levels in the patient (before & after treatment) and control group

Parameters	Patient group (Mean ± SD)(n=55)		Control group (Mean ± SD)(n=30)	ReferenceValues
	Before treatment	After treatment		
TSH (mIU/L)	60.0 ± 31.7	3.3 ± 4.2	1.6±1.4	0.4 – 5.0
FT_4 (pmol/L)	5.4 ± 2.9	17.1 ± 4.4		9.1 – 23.8

(M ±SD) of total cholesterol (TC), LDL cholesterol (LDL-C) & triglyceride (TG) of patient group (before treatment) were231.6 ± 62.9mg/dl, 152.4 ± 59.4mg/dl & 186.9 ± 95.3mg/dl respectively. On the other hand (M±SD) of TC, LDL-C & TG of control group were 146.9 ± 23.6 mg/dl, 70.6 ± 25.6 mg/dl & 100.5±39.2mg/dl respectively. (M±SD) of HDL-C of the patient group and control group was 41.4±3.8mg/dl & 56.3±11.5mg/dl respectively. TC (p=0.000), LDL-C (p=0.000), TG (p=0.000) were significantly higher but HDL-C (p=0.000) was significantly lower in the patient group compared to control group (Table-3). In forty five (81.8%) subjects, HDL-C were below NCEP/ATP-III target and in twenty one (38.1%) subjects, LDL-C were above NCEP/ATP-III target.

In the final follow-up (at the end of 3rd month after euthyroid state with thyroxine) (M±SD)TC, LDL-C & TG levels of the patient group were 196.6±38.4mg/dl, 122.7±33.1mg/dl & 163.3±81.7mg/dl respectively. (M±SD) HDL-C was 40.2±6.1mg/dl. After treatment with thyroxine there was significant reduction in TC (p=0.000) & LDL-C (p=0.000) but TG (p=0.057) & HDL-C (p=0.217) did not change significantly (Table-4).

In eight (14.5%) subjects, LDL-C levels remained above NCEP/ATP-III target. After LT4 therapy LDL-C was significantly reduced (X^2=7.9, P< 0.01) (Table-5).

TSH always showed positive correlation with total cholesterol (r=0.276, p=0.041) & LDL- cholesterol (r=0.306, p=0.022) and no correlation with triglyceride (r=0.002, p=0.986) & HDL- cholesterol (r= -0.070, p=0.610) (Table-6).

FT_4 showed no correlation with total cholesterol (r= -0.229, p=0.126), LDL- cholesterol (r= -0.212, p=0.158), triglyceride (r= -0.146, p=0.334) & HDL- cholesterol (r=0.280, p=0.060) (Table-7).

Table-III

Lipid profile in the patient group (before treatment) & Control group

Parameters	Patient group (Before treatment) (Mean ± SD)(n=55)	Control group (Mean ± SD)(n=30)	p-Values
Total Cholesterol120-200mg/dl	231.6±62.9	146.9±23.6	0.000
HDL CholesterolM=>40mg/dlF=>50mg/dl	41.4±3.8	56.3±11.5	0.000
LDL Cholesterol<130mg/dl	152.4±59.4	70.6±25.6	0.000
Triglyceride<150mg/dl	186.9±95.3	100.5±39.2	0.000

Table-IV

Paired t-test of Lipid profile between patient group (before & after treatment)

Parameters	Before treatment (Mean ± SD)(n=55)	After treatment (Mean ± SD)(n=55)	p-Value
Total Cholesterol	231.6±62.9	196.6±38.4	0.000
HDL Cholesterol	41.4±3.8	40.2±6.1	0.217
LDL Cholesterol	152.4±59.4	122.7±33.1	0.000
Triglyceride	186.9±95.3	163.3±81.7	0.057

Table-V

Shows changes of LDL-C after LT_4 therapy

Groups	LDL-C level above NCEP/ ATP-III target	LDL-C level below NCEP/ ATP-III target	N
Before treatment	21	34	55
After treatment	8	47	55
Total	29	81	110

c^2 = 7.9, P < 0.01

Table-VI

Correlation between TSH levels and lipid profile of the patient group (before treatment)

Parameters	Lipid Profile(Mean ± SD) (mg/dl)		r-value	p-Value
TSH (Mean ± SD) 60.04±31.79(miu/L)	Total Cholesterol	231.6±62.9	0.276	0.041
	HDL Cholesterol	41.4±3.8	-0.070	0.610
	LDL Cholesterol	152.4±59.4	0.306	0.022
	Triglyceride	186.9±95.3	0.002	0.986

Table-VII

Correlation between FT_4 levels and lipid profile of the patient group (before treatment)

Parameters	Lipid Profile(Mean ± SD) (mg/dl)		r-value	p-Value
FT_4 (Mean ± SD) 5.47±2.94(pmol/L)	Total Cholesterol	231.6±62.9	-0.229	0.126
	HDL Cholesterol	41.4±3.8	0.280	0.060
	LDL Cholesterol	152.4±59.4	-0.212	0.158
	Triglyceride	186.9±95.3	-0.146	0.334

Discussion

Hypothyroidism is a common hormonal disorder in the general population, especially in older women. 9.5% of the participants of the Colorado prevalence study had elevated levels of thyroid stimulating hormone[13]. Levels of TC and LDL-C tend to increase as the thyroid function declines. Therefore, hypothyroidism constitutes a significant cause of secondary dyslipidemia,[4]. Pazos et al[10] observed that at diagnosis most of the hypothyroid patients had increased plasma concentration of TC, LDL-C and apo-B, and treatment resulted in a progressive decrease in all of these parameters. Klausen et al[11] reported that elevation of plasma total cholesterol was a frequent finding in untreated hypothyroid patients, probably due to impaired LDL-cholesterol catabolism secondary to a reduced number of LDL-receptors. Arem et al[12] found that both overt and sub-clinical hypothyroid patients were associated with lipid abnormalities in the form of increased TC, LDL-C and lipoprotein (a). Staub et al[14] also concluded that the magnitude of changes in lipoprotein fractions in hypothyroid patients correlate with severity of thyroid hormone deficiency. Hemiberg et al[15] have stated that hypothyroidism was associated with elevation of TC, LDL-C and HDL cholesterol[16], although in some studies HDL-C was reduced[15,17]. Furthermore anti-thyroid therapy raised HDL-C. Administration LT4 produced inconsistent changes in HDL-C, sometime increasing, decreasing or not changing. Pazos et al[10] studied 12 severely hypothyroid patients before and after L-thyroxine replacement. They found that at diagnosis, most of the patients had increased plasma concentration of TC, LDL-C and apo-B, and treatment resulted in a progressive decrease in all of these parameters. But TG levels did not change significantly at any time. The HDL-C concentration fell slightly during treatment . Klausen et al[11]studied 13 patients with symptomatic primary hypothyroidism before and during LT4 therapy. They observed that treatment resulted in a significant decrease in TC, LDL-C and HDL-C. The triglyceride levels did not change significantly. Arem et al[12] enrolled 15 patients with overt hypothyroidism and 14 patients with sub-clinical hypothyroidism. They measured fasting lipid level initially and 4 months after achievement of a euthyroid state with incremental L-thyroxine therapy. In the overtly hypothyroid group, restoration of the euthyroid state was associated with a significant reduction in TC, LDL-C, apoAI and apoB-100. Present study was designed to see the effect of L-thyroxine on serum lipoproteins abnormalities in hypothyroid patients. It was observed that mean of TC, LDL-C and TG of patients group (before treatment) were significantly higher than control group. On the other hand mean of HDL-C was significantly lower in the patient group compared to control group. After treatment with L-thyroxine there was significantly reduction in TC & LDL-C but there was no significant change in TG & HDL-C.In the present study control subjects were taken to compare the lipoproteins between general populations and hypothyroid patients.In our study, pre-treatment value of TC, LDL-C and TG were found significantly higher compared to control which is similar with the findings of earlier studies[6,10,12]. After LT4 therapy there is significant reduction of TC and LDL-C which is also consistent with the previous studies[10,11,12]. Serum TG level after LT4 therapy is decreased but not statistically significant in the present study which is comparable with the earlier studies[15]. HDL-C is lower in hypothyroid patients compared to control which is consistent with previous findings[13]. After LT4 treatment HDL-C does not changed significantly which is also consistent with previous studies[17]. In the present study TG was found reduced but not statistically significant after LT4 therapy. This findings is inconsistent with the previous studies were done by Pazos et al[10] and klausen et al[11], but consistent with the findings of Mules et al[18]. In our country high TG and low HDL may be due to genetic factors or high consumption of carbohydrate . So our study regarding the effect of LT4 therapy on TG is consistent with some studies and inconsistent with the others. So large scale and long time study may be done for final decision.

Conclusion

1) Hypothyroid patients have lipid abnormalities in the form of high TC, LDL-C, TG and low HDL-C.
2) Therapy with L-thyroxine reduces total-cholesterol and LDL-cholesterol levels but has no significant effect on triglyceride and HDL-cholesterol.

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REVIEW ARTICLE

IVERMECTIN: A PROMISING THERAPEUTIC WEAPON TO COMBAT PARASITIC INFECTIONS

HK PAUL[1], ASM ZAKARIA[1], ATM ASADUZZAMAN[1], MT ISLAM[2], AM CHOUDHURY[1], AZMM ISLAM[1]

Summary

Ivermectin (IVM), is a macrocyclic lactone produced by the soil actinomycete, streptomyces avermitilis, devoid of antibacterial activity that acts strongly against a wide variety of insect, nematode & acarine parasites of animals and humans. It is a safe and effective therapeutic agent that may open a new era in the treatment of parasitic skin diseases particularly for patients with scabies. Before it's full potential in Dermatology can be assessed, more clinical exposure in treating parasitic diseases are needed.

Introduction

In 1970s, during an intensive search for natural substances with anthelmintic properties, over 40,000 cultures of actinimycetes were screened in collaboration between the Kitasato Institute in Japan and the Merck Institute for Therapeutic Research in the United States. Streptomyces avermitilis, isolated from Japanese soil, was the only organism tested that produced a class of compounds known as avermectins. One of these, avermectinB_1 (abamectin), was later chemically modified to form ivermectin, a macrocyclic lactone structurally similar to the macrolide antibiotics but devoid of any antibacterial activity. Ivermectin did, however, act strongly against a wide variety of insect, nematode & acarine parasites of animals and humans. Ivermectin is used worldwide to control these infections and infestations, including sarcoptic mange in domesticated animals. In veterinary medicine, it is formulated for both topical and oral delivery, for administration in feed, and as a subcutaneous injection. In humans, ivermectin has been used extensively since 1987 to control onchocerciasis, a disfiguring and blinding disease caused by the filarial worm Onchocerca volvulus in the countries of Africa and Latin America where the is endemic[1,2].

The United States Food and Drug Administration has licensed ivermectin for the treatment of onchocerciasis and strongyloidiasis but not for the scabies. However, since 1993, it has been successfully used in other countries to treat human scabies resistant to other treatment[3]. The drug is also effective in the treatment and chemoprophyllaxis of other filariasis such as loiasis and bancroftian filariasis and other intestinal nematodes, mainly strongyloidiasis[4].

The interest of Dermatologist in ivermectin grew as it became evident that some parasitic infections in humans with cutaneous tropism could easily and successfully be treated with the drug either orally or topically[5]. The aim of the review is to summarize the current knowledge regarding the therapeutic action of Ivermectin in parasitic diseases and to give an outlook for the putative indication in future.

Mechanism of action

Ivermectin, a member of a family of macrocyclic lactone, the avermectins, has a broad spectrum of activity against parasites. It binds to glutamate-gated chloride channels, which are present in invertebrate nerve and muscle cells, causing paralysis and the death of the parasite. It does not easily cross the blood-barrier in human and has low affinity for mammalian ligand gated chloride channels. Ivermectin acts only at certain stages of life cycle of parasite[6,7,8]. Although Ivermectin is believed to act mainly through interactions with invertebrate glutamate-gated chloride channel, other targets such as spleen cells and aminobutyric acid receptors may play important roles in it's anti-parasitic activity[9].

Pharmacology

Ivermectin has a empiric formula of $C_{48}H_{74}O_{14.}$ Absorption is not well studied. After a single dose of ivermectin mean peak plasma concentration peaks at 4 hours. The drug is extensively metabolized in liver. Excretion primarily occurs in feces within next 10-14 days. Plasma half-life is approximately16 hours[10]. As several organisms have evolved

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resistance to ivermectin through mutations in p-glycoproteins and/or the glutamate-gated chloride channel itself, research continues on improvement of IVM either through mode of administration or the feasibility of alternative macrolides. An understanding of IVM's pharmacology is essential before improved therapeutics are created.[9]It is available as 3mg/6mg tablets in our country.

Clinical uses

Ivermectin is the drug of choice for a variety of parasitic diseases due to its broad spectrum of activity and wide margin of safety. More than 18 million people are treated with Ivermectin each year. Delivery modes include oral, topical, and s.c. injections. Its anti-parasitic activity depends upon species and developmental stages[9].

Dourmishev AL et al. reported that Ivermectin is effective against a series of endoparasites with cutaneous tropism such as Strongyloides stercoralis, Ancylostoma braziliense, Cochliomyia hominivorax, Dermatobia hominis, Wuchereria bancrofti, Brugia malayi, Brugia timori, Onchocerca volvulus, Loa-loa and ectoparasites such as Sarcoptes scabies, Pediculus humanus, Demodex folliculorum, and Cheyletiella sp[11].

Onchocerciasis: Greene BM et al. and Greene BM et al. reported that ivermectin has been used to control onchocerciasis, a disfiguring and blinding disease caused by filarial worm onchocerca volvulus[12,13]. It is estimated that more than 6 million people in over 30 countries have been treated with ivermectin to control this disease, for which over 30 million people are considered to be at risk[14].

Scabies: Oral ivermectin offers several advantages over standard topical scabicides. The treatment is easy, safe and well tolerated with maximal patient compliance. In contrast, the efficacy of topical therapy depends on compliance; clinical form and possibly resistance. Effective topical therapy requires thorough application over the body and may cause side effect like burning sensations and dermatitis[15]. Meinking TL et al. reported that of 11 patients with scabies 45% were cured by 2 weeks and rest were cured by 4 weeks after single dose of oral ivermectin. Out of 11 human immunodeficiency virus (HIV)-positive cases reported clinical cure rate was 73% with single dose of ivermectin and greater than 90% cured with two doses of ivermectin.[1]

Crusted scabies: A severe form of scabies with high mite burden usually associated with an underlying immunosuppression, may require repeated application of topical scabicides. Single dose of ivermectin, 200µg/kg is effective in some cases but most commonly 2 or 3 doses separated by interval of 1or 2 weeks are required. In some cases the drug permitted recovery of crusted scabies refractory to topical conventional scabicides[16].

Table-I

Some of the diseases, causative agent and treatment schedule with oral ivermectin.

Disease	Causative agent	Dose/day	Duration of treatment
Cutaneous larva migrans	Ancylostoma braziliense & A. caninum	200µg/kg	1-2days[17]
Gnathostomiasis	Gnathostoma spinigerum & other gnathostoma species	200µg/kg	1-2 days[17]
Strongyloidiasis/Larva currens	Strongyloides stercoralis	200µg/kg	1-2 days[17,18]
Onchocerciasis	Onchocerca volvulus	150µg/kg	Once & repeated every 6-12 months until asymptomatic[17]
Filariasis	Wuchereria bancrofti, Brugia malayi, B.timori	200µg/kg	Single dose to reduce/ suppress microfilaremia[17]
loiasis	Loa loa	200µg/kg	
Pediculosis	Pediculus humanus	200µg/kg	2 doses given 10 days apart[18]
Scabies	Sarcoptes scabiei	200µg/kg	Single dose, can be repeated after 7-10 days [17, 19]
Crusted scabies	Sarcoptes scabiei	200µg/kg	2-3 doses, 7/14 days part[18,19]

Use in children

Safety not proved in children weighing below 15 kg (33 lb) [20]

Use in pregnancy

The pregnancy prescribing status of ivermectin is category C[10]

Adverse reactions

More than 18 million people are treated with Ivermectin each year for various parasitic infestations[9]. No serious drug-related adverse events have been reported. Side effects of ivermectin include fever, headache, chills, arthralgia, rash, eosinophilia, and anorexia. Many of these symptoms are thought to result from the death of parasites rather than as a reaction to the drug[20]. The drug appears to have good margin of safety, although neurotoxicity may be possible[19].

Ivermectin seems to be concentrated in the liver and fat tissue, with very low levels reaching the central nervous system. No significant drug interactions have been reported.[20] There are concerns regarding its use in young children and pregnant women, because there may be more drug penetrance of the immature blood-brain barrier[20].

del Giudice P et al. reported that elderly nursing home patients treated for scabies infection showed an increased death rate among ivermectin-treated patients, but it was noted that this finding has not been confirmed in multiple subsequent trials[2].

Drug interactions

There is no drug interactions known involving oral ivermectin therapy[10].

Conclusion

Available evidence suggests that Ivermectin may open a new era in dermato-pharmacology. Single oral dose of ivermectin might be used as a public health measure to control wide spread scabies in population group. However safety in children weighing below 15 kg and in elderly patients is not established. Due to resistance to topical therapy ectoparasitic infestations are increasingly becoming important and Ivermectin might be an advance therapeutic armamentarium in these cases. Moreover, it may fulfill the dream of a unique treatment of the most human ectoparasites in future.

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CASE REPORTS

ADULT STILL'S DISEASE : CASE REPORT WITH A BRIEF REVIEW

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Summary

Adult Still's disease (ASD) is a rare rheumatological disorder which commonly presents with high spiking fever with polyarthritis. It is an important cause of PUO and is easily missed. High level of clinical suspicion is the key to diagnosis of ASD. Here we report 3 cases of ASD, all of the cases were suspected to be infectious disease and treated accordingly without any response.

Introduction:

Adult Still's disease (ASD) or adult onset Still's disease (AOSD) is an important cause of pyrexia of unknown origin (PUO). About 5% patients with PUO have ASD.[1] Typical presentation is with high grade fever, joint pain, skin rash, lymphadenopathy and hepatoslpenomegaly.[2] Raised acute phase reactants, high WBC count, elevated liver enzymes and very high ferritin levels are common.[3] But none of these are sufficient to establish the diagnosis and ASD is a disease of exclusion.[2]

Case report:

Case 1:

A young man of 24 years was admitted in BSMMU on May 1, 2008 with the complaints of fever, cough, anorexia, bodyache, headache and significant weight loss for 2 months. Fever was high grade (highest 105° F), initially intermittent, but later continued, without any chill or rigor. There was no traveling history. Cough was initially dry, later mucopurulent, without haemoptysis. He had pain and swelling of right knee joint for 15 days. Chest x-ray showed right paratracheal lymphadenopahy. He was treated with several antibiotics and NSAID by general practitioners and in private clinics, but his condition didn't improve. Finally, he was referred to BSMMU for further management.

Findings on admission in BSMMU: Patient was mildly anaemic, emaciated, pulse 120/min, BP 100/70 mm Hg, temperature 103° F, right sided cervical lymphadenopathy, largest 1 X 2 cm, firm, nontender, mobile and without sinus and 1 cm splenomegaly. Right knee joint was swollen and tender. Other systems revealed no abnormalities.

Investigations: Hb 10 gm/dl, TC 21,000/cmm (80% neutrophils), ESR 95 mm in 1st hour, urine normal, RBS 5.5 mmol/L. Blood C/S, RA factor and ANA were all negative. MT 02 mm. Sputum C/S showed Gram positive cocci. Chest x-ray showed right paratracheal lymphadenopathy with ill-homogeneous opacity in apical zone. Serum ferritin was > 2,100 mg/ml (normal value 40 to 200 mg/ml).

After giving I/V ceftriaxone and oral clarithromycin for 7 days, opacity in chest x-ray disappeared, but paratracheal lymphadenopathy persisted and fever did not subside. Repeat ferritin showed 8,000 mg/ml. I/V dexamethasone was started along with other supportive treatment. Both pain and fever subsided in 3 days. The final diagnosis was adult Still's disease. The patient was discharged with 60 mg prednisolone daily. On follow up, the patient was afebrile and found to be absolutely fine.

Case 2:

A 32 year old female was admitted in Central Hospital on July, 2007 for three months history of high grade continued fever, polyarthritis, anorexia, weakness, exhaustion, occasional abdominal pain and weight loss. Initially, she was treated by private practitioners and also in a hospital. Enteric fever was suspected and lots of antibiotics, including ciprofloxacin, azithromycin and ceftriaxone etc. were given, but her fever and other symptoms did not subside. So, she was referred to Central Hospital for better management.

Examination revealed mild anaemia, pulse 116/min, BP 115/60 mm Hg, temperature 104°F and mild hepatosplenomegaly. Wrists, elbows, right shoulder and right knee were swollen and tender. Other

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systems were normal. Investigations showed Hb 9.3 gm/dl, TC 25,000/cmm (88% neutrophil), ESR 130 mm in 1st hour and platelet 4,50,000/cmm. Widal test showed TO: 160. Urine showed 6 to 7 pus cells/HPF. Blood and urine C/S, RA, ANA and anti ds-DNA were negative. Chest x-ray was normal. USG of abdomen showed mild hepatosplenomegaly. Serum ferritin was > 10,000 mg/ml.

A diagnosis of adult Still's disease was established. Due to her poor general condition and inability to eat, she was given I/V dexamethasone for 5 days with other symptomatic treatment like IV 5% DNS, paracetamol, omeprazole etc. Both fever and arthritis subsided. She was discharged with prednisolone 60 mg daily, gradually tapered after 2 weeks, and methotrexate 7.5 mg weekly. On follow up visits, she was doing very well.

Case 3:

A young man of 36 years, working in Kingdom of Saudi Arabia, returned to Bangladesh due to unexplained fever. According to his statement, he had high grade continued fever for 4 months along with anorexia, vomiting, occasional loose motion, severe weakness and loss of about 10 kg body weight. He was admitted in a hospital in KSA. Investigations in KSA showed nothing significant. There was only leukocytosis with raised ESR. Brucellosis and HIV were negative. He was treated with several broad spectrum antibiotics, but his symptoms did not subside. So, he returned to Bangladesh and got himself admitted in Central Hospital.

After admission, he was found ill looking, emaciated, pulse 122/min, BP 100/70 mm Hg, temperature 104°F. He had bilateral cervical lymphadenopathy and splenomegaly. Other systems revealed normal findings.

Investigation: Hb 10.4 gm/dl, TC 17,000/cmm (88% neutrophil), platelet 4,00,000/cmm, ESR 140 mm in 1st hour and urine normal. Blood and urine C/S, MT, MP and ICT for kala azar were negative. Chest x-ray showed right paratracheal lymphadenopathy. Ultrasonogram of abdomen showed splenomegaly. Lymphnode FNAC showed paracortical immunoblastic hyperplasia. Serum ferritin was > 3,000 mg/ml.

A diagnosis of adult Still's disease was made. Since the patient was unable to eat, he was treated with I/V dexamethasone for 5 days and other symptomatic treatment like IV fluid, B complex, omeprazole etc., followed by oral prednisolone 60 mg/day. The patient responded and symptoms subsided quickly.

Discussion:

Adult Still's disease is rare[4] and in the setting of PUO, a high degree of clinical suspicion is needed.[1] In all these cases, patients were initially thought to be suffering from infectious diseases and treated with broad spectrum antibiotics empirically without any definite diagnosis. In each case, the patient did not respond. After excluding other probable diagnoses and due to the presence of very high serum ferritin, ASD was a prime suspect in these patients. All of them responded well to steroid. This shows the importance of a complete clinical and laboratory work up in all cases with unexplained fever.

Review of literature:

In 1896, George Still described a condition in children with high fever, arthritis and evanescent rash. This "Still's disease" was later known as systemic onset juvenile inflammatory arthritis.[5] In 1971, the term "Adult Still's Disease" (ASD) was used to describe adult patient who had features similar to Still's disease in children and did not fulfill the criteria for rheumatoid arthritis.[6] It is a rare rheumatic condition characterized by high fever, arthritis, polyserositis and typical skin rash.[2]

The cause of ASD is unknown, though some infectious triggers like EBV, herpes virus, *Mycoplasma pneumoniae* etc. and some genetic factors have been suggested.[3,7] The incidence is 1 to 3 cases per million per year with equal sex distribution.[4] Age distribution showed two peaks, one between 15 and 25 years, the other between 36 and 46 years.[7]

A quotidian or double-quotidian high grade **fever** with a short peak in the evening, recurring for several days is the hallmark of ASD.[2,5] An evanescent, salmon-pink, macular or maculopapular, nonpruritic **rash** predominantly involving the trunk and proximal extremities, usually appears with fever. **Arthralgia and arthritis** commonly involve the knees, wrists, ankles, elbows, proximal interphalangeal joints and shoulders. Arthritis is initially mild, transient and oligoarticular, but gradually becomes severe, destructive and polyarticular.[8] There may be severe and debilitating **myalgia** coinciding with fever, without any weakness. Other common features which include severe non-suppurative **pharyngitis**, tender **lymphadenopathy**, **hepatosplenomegaly** and **abdominal pain**. Pericarditis, pleural effusion, transient pulmonary infiltrates may occur (30-40% cases). Other cardiopulmonary complications include severe ILD, ARDS and myocarditis leading to arrhythmia and heart failure.[9,10]

Three clinical courses of ASD have been described. One third patients have a monophasic pattern lasting less than one year with complete resolution. Another one third have a polycyclic or intermittent course with

complete remission between flares. The remaining patients have a chronic course of ASD with persistently active disease, usually due to a chronic, destructive arthritis.[3] This evolution of the disease is unpredictable.[11]

Elevated **acute phase reactants** are universal in ASD.[3] Both **ESR** and **CRP** are increased. **Peripheral blood** picture shows TC>15,000 cells/cmm (mostly granulocytes), Hb 10 gm/dl or less, RBC normocytic and normochromic and platelet count is 400000/cmm or more. Serum **aminotransferases** and **lactate dehydrogenase** are elevated in 75%.[3] Serum **ferritin** is markedly elevated in 70% cases.[7] It may be more than 3,000 ng/ml (normal 40-200 ng/ml). Some patients even have values above 10,000 ng/ml, but normal level of ferritin does not exclude ASD.[12] On remission of ASD, serum ferritin level becomes normal.[13] **RA factor** and **ANA** are negative, but a low titre of either test may occur in upto 10% cases and may obscure the diagnosis.[3]

X-ray shows non-erosive narrowing of carpometacarpal and intercarpal joint spaces of the wrist, which often progresses to bony ankylosis.[3]

Skin biopsy may help to differentiate ASD from vasculitis or Sweet's syndrome. It shows mild perivascular inflammation of the superficial dermis, consisting primarily of lymphocytes and histiocytes, and dermal edema. Immunofluorescence of skin biopsy may show slight deposition of C3 in the blood vessel wall.[8] The **synovial fluid** is usually inflammatory with a mean leukocyte count of 13,000 cells/cmm. Synovial biopsy reveals a chronic synovitis with slight cell proliferation in the synovial lining layer, moderate vascular engorgement and a mononuclear cell infiltrate.[3] **Lymph node biopsy** typically shows intense, paracortical immunoblastic hyperplasia, which is distinct from the changes observed with rheumatoid arthritis, SLE or Sjogren's syndrome.[14] Immunohistochemistry reveals a benign, polyclonal B-cell hyperplasia, which distinguishes ASD form lymphoma.[15]

In the absence of any specific laboratory test, at least 7 sets of diagnostic criteria have been proposed. Of which, Yamaguchi criteria[16] has the highest sensitivity (93%)[17]. Here the **major criteria** are – fever of at least 39°C for 1 week or more, arthralgias or arthritis for 2 weeks or more, typical rash and WBC 10,000/cmm or more with at least 80% granulocytes. **Minor criterias** are as follows, such as– sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function test and negative tests for ANA and RA factor. Presence of 5 criteria, of which at least 2 are major, is needed for diagnosis of ASD. The presence of any infection (e.g. IMN), malignancy (e.g. lymphoma) and other rheumatic diseases that may mimic ASD (e.g. PAN, SLE), which should be excluded.

Initially, NSAID may be used in patient with mild disease, but if there is no response within several days, glucocorticoid should be added. Patient with very high fever, joint destruction or internal organ involvement should get steroid from the beginning.[3,18] Usual dose of prednisolone is 0.5 to 1.0 mg/kg/day, gradually reduced over several months. A low maintenance dose might be needed for several years. Pulse methylprednisolone (e.g. 1000 mg/day for three days) is used for life threatening cases. 70% of patients respond to glucocorticoid.[19]

In refractory cases, biological agents should be added. Drugs in this category that are used are anti-TNF alpha agents (eg infliximab, adalimumab, etanercept), anakinra and rituximab.[20,21,22] DMARDs are used when patients don't respond sufficiently to previous modalities, or develop unacceptable side effects. Hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide, leflunomide, cyclosporine, sulfasalazine, IV immunoglobulin, etc. have been tried, but the efficacy is not proven yet.[3,23,24]

Functional status in ASD generally stays very good. Predictors of bad prognosis include early development of polyarthritis, involvement of root joints (shoulders or hips) and the need for more than two years of systemic steroid therapy.[3,18]

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SPLENIC TUBERCULOSIS: A CASE REPORT

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Introduction

Splenic abscess is a rare clinical entity with an incidence of 0.2 to 0.7% in autopsy-based studies[1,2]. Among them splenic tubercular abscess is a very rare clinical entity. This form of tuberculosis is normally seen as a part of miliary tuberculosis and is rarely an isolated entity. Tuberculosis continues to be a major health hazard, inspite of notable advances in its diagnosis and treatment[3]. This systemic disease presents with varied clinical manifestations as pulmonary tuberculosis or extra pulmonary tuberculosis. Extra pulmonary tuberculosis accounts for almost 15% of all cases of tuberculosis. Here we are reporting a case of splenic tuberculosis which presented as an isolated entity.

Case report

A 55–year-old diabetic patient presented with pain in the left hypochondrium with irregular fever and loss of weight for 18 months. Before admission, he had treatment without having any definite diagnosis. He neither had any significant illness apart from diabetes mellitus nor had any contact with a patient of tuberculosis or HIV. On admission, he was febrile (temperature was 101^0- F) slightly anaemic and was normotensive. There was mild tenderness over the left hypochondrium. Liver and spleen were not palpable.

He was not in glycemic control. His fasting and post prandial blood glucose were 16.9 mmol/l and 32.5 mmol/l respectively. His haemoglobin was 09.4 g/dl, TLC 13.8 x 10^9/L, DLC: N = 73%, L = 19%, E = 01%, M = 07%, and ESR 100 mm in first hour. Radiograph of chest (PA view) did not show any abnormality. Urinalysis and other biochemical parameters were within normal limits. Ultrasonograpy revealed multiple mixed echogenic lesions of variable size in the spleen suggesting multiple abscess or lymphomatous deposits. On CT guided FNAC frank pus came out; the smear showed numerous pus cells, macrophages and degenerated cells. Acid fast bacilli were not seen. After achieving glycemic control with shot acting insulin, correction of anaemia and proper vaccination splenectomy was performed. The cut section surface showed multiple gray white areas, some of which contained pus like material.

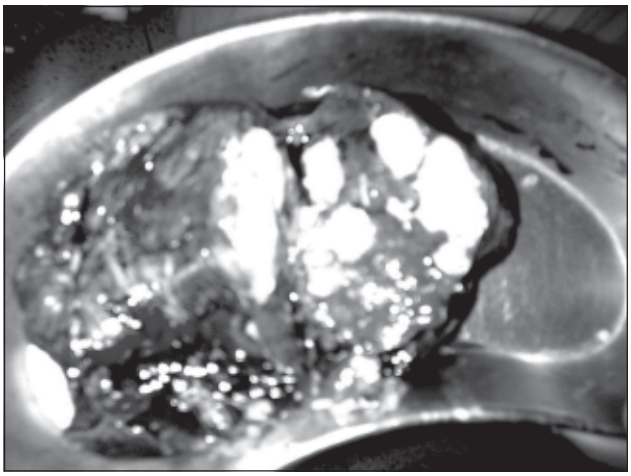

Fig1. *Cut section of the spleen showing multiple gray white areas, some of which contain pus like material.*

Formalin fixed paraffin embedded sections showed collection of epithelioid cells, Langhans' giant cells and areas of caseation necrosis.

A diagnosis of tuberculosis of the spleen was made. The patient is on four drug regimen anti-tuberculosis chemotherapy and is doing well till date.

Discussion

Splenic abscess can be classified in several ways. Lawhone and Zuidima[4] divided them in two groups, unilocular splenic abscess, generally diagnosed clinically and multilocular splenic abscess usually small and found at autopsy. The most accepted classification is that of Chun and Colleagues[5] who divided splenic abscess according to the predisposing cause- Primary pyogenic abscess, after the splenic trauma, in patient with haemoglobinopathies and due to contiguous disease affecting the spleen.

Splenic abscesses have diverse aetiologies[1]. The presence of a septic focus in some part of the spleen is the most frequent cause of splenic abscess[6]. In the pre –antibiotic era the splenic abscess was mainly related to typhoid fever, malaria or amoebic dysentery[7]. Today the most frequent cause is bacterial endocarditic ranging from 10% to 20 % of causes[5] followed by urinary tract infection. Splenic abscess also has been noticed after dental extraction, appendicitis, prostatectomy or gastrointestinal surgery among other causes[5].

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In most cases, splenic abscesses present insiduously with fever (92.5%), left upper abdominal pain (39.2%), pleuritic chest pain (15.8%), and malaise being the common symptoms. Left upper quadrant tenderness (38.2%) and splenomegaly (56.0%) are the most frequently encountered signs on examination[8]. Leucocytosis is invariably present in all patients. Almost all patients have an abnormal chest skiagram with left sided findings, e.g., pleural effusion, lower lobe atelectasis, or elevated hemidiaphragm, observed in 80% of patients[9,10]. In 25% of patients, abnormal displacement of gastric shadow or extra - alimentary gas in the left upper quadrant may be seen on a plain X-ray of the abdomen. Ultrasonography of the abdomen demonstrates hypoechoic (87%) or anechoic (13%) lesions in the spleen, outlined in most cases by irregular walls[9,10]. A CT Scan of the abdomen is the most reliable tool for the diagnosis of a splenic abscess, which appears as a low density mass lesion with peripheral enhancement after intravenous contrast. The presence of a gas or fluid level within the spleen is diagnostic of a splenic abscess. The CT Scan, by delineating the exact location of an abscess, also helps in planning therapeutic strategies like percutaneous drainage.Technetium 99 m (99 m Tc) and Gallium – 67 Scans are also sensitive, though less specific tools for the diagnosis of a splenic abscess.

The possible ways of involvement of the spleen in tuberculosis may be (i) miliary tuberculosis, (ii) generalised caseatng tuberculous lymphadenitis and (iii) acute non-reactive haematogenous tuberculosis[11]. Splenic tuberculosis occurs in two forms. The first is its involvement during miliary tuberculosis especially in immunocompromised patients, which is not rare and it's treatment includes classic antituberculous treatment, and if possible improving patient's immunity. This form needs surgical intervention as an exception[12]. Spleen is the third organ becoming involved in miliary T.B. (lung 100%, liver 82%, spleen 75%, lymph nodes 55%, bone marrow 41%)[13]. Many reported cases of splenic tubercular abscess are found to have underlying HIV infection also[3]. The second form is the primary involvement of spleen which is extremely rare (the same as our patient). In English, French and German literature, from 1965 to 1992, just six cases were reported[14]. These patients were immunocompetent[15] and there was usually another site involved by T.B. Adil A et al[16] reported a series of 10 immunocompetent individuals with splenic tuberculosis

The presentation of these cases was fever of unknown origin (FUO), in most of them final diagnosis was made by laparotomy, although CT guided splenic puncture is becoming a more ideal and popular method nowadays[16]. In differential diagnosis of CT findings, lymphoma, hydatid disease and metastases must be considered[17]. In conclusion: despite its rarity, splenic tuberculosis must be considered in patients, with FUO and splenomegaly.

Our single experience shows that tuberculous splenic abscesses could be treated with early splenectomy which has been suggested by some authors seems [18,19] followed by oral antituberculous drugs.

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