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EDITORIAL

ORIGINAL ARTICLES

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EDITORIAL

MELIOIDOSIS

Manoj Kumar Mohapatra

Melioidosis is caused by *BurkholderiaPseudomallei*, a facultative intracellular organism that replicates inside macrophages and polymorphonuclear leukocytes. It is found in soil and water. Humans and animals are infected by the organism by inoculation, inhalation, or ingestion. Rarely it is transmitted from man to man. This is restricted to South-East Asia, northern part of Australia, with occasional reports from India and China[1]. One such case has been reported here in this issue of OPJ.[2]

B.Pseudomallei causes a wide spectrum of disease. It may cause asymptomatic infection, abscess formation, fatal community acquired pneumonia, disseminated diseases, and septicemia in endemic areas. Pulmonary infection is the most commonly diagnosed form of melioidosis[1,3]. Acute pulmonary infection is most common clinical presentation. Pneumonia may be asymptomatic or may present with severe necrotizing disease. The former is diagnosed with routine chest X- ray with upper-lobe affection. *B.Pseudomallei* can cause chronic pulmonary infections with systemic manifestations that mimic pulmonary tuberculosis, including chronic cough, fever, hemoptysis, night sweats, and cavitarylung disease.

Apart from pulmonary manifestations melioidosis, also can cause skin ulceration with associated lymphangitis and regional lymphadenopathy. In septicemic form of melioidosis, infection spreads from skin or lungs and causes high mortality up to 44.0%[2].

This disease is found commonly among patients with diabetes mellitus, renal disease, HIV infection, neoplasia. It may be found in normal healthy persons. Bacteriological diagnosis is the key for the diagnosis.

The treatment of melioidosis is prolonged. It is divided into two stages: an intensive stage and maintenance stage. Intensive stage is treated with injectable Ceftazidime (2 gm. 6 hourly) or Meropenem (1 gm. 8 hurly), or Imipenem (500 mg. 6 hourly) for 2 weeks. It is followed by maintenance phase with trimethoprim-sulfamethixazole (1600/320 mg 12 hourly) for 3 months[1].

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Original article

N-TERMINAL PRO-BNP : A PROGNOSTIC MARKER FOR HOSPITAL OUTCOME OF CONGESTIVE HEART FAILURE

Jan Ahamed*, Diptimayee Tripathy**, S.N Jali***, R.N .Raut****

ABSTRACT

***Backgrou**nd: Congestive cardiac failure is one of the leading cause of morbidity and mortality in the populations across the globe[1].Despite great advances in medical management, the prognosis remains poor. NT-proBNP is a neurohormone which is stored mainly in the myocytes of the ventricle and released as a result of pressure and volume overload or myocardial damage. BNP levels have been reported to be strong independent predictors of early re admission or death due to HF.**Methods**:It is a hospital based prospective study with 35 patients admitted in the General Medicine wards and in the cardiology ward of MKCG Medical College and Hospital, Berhampur, Odisha who had clinical evidence of congestive heart failure according to Framinghams criteria[2] and confirmed by 2D echocardiography.**Results**: Mean NT-proBNP levels of NYHA class I,II,III and IV are 2950.67,4578.61,5215.82 and 6262.67 pg/ml respectively. There is strong correlation between NYHA classes I and II; and III and IV with the mean NT-proBNP levels with r=0.7983, p<0.0001 and r=0.9366, p<0.0001. The receiver-operating characteristic curve showed that the threshold value of NT-proBNP at the admission day and the seventh post admission day having the highest sensitivity and specificity for predicting adverse hospital outcome was 5351 pg/ml (70% and 71%) and 2542 pg/ml (62% and 71%) respectively.Out of the two values, NT-proBNP levels at admission has more prognostic and predictive value since it has more specificity and sensitivity compared to the seventh day values.**Conclusion:** This study establishes the role of NT-proBNP as a prognostic marker of hospital outcome in patients with congestive heart failure. This also demonstrated a steady correlation of NT-proBNP levels with both NYHA class and left ventricular ejection fraction in patients with heart failure.*

INTRODUCTION

Congestive cardiac failure is one of the leading cause of morbidity and mortality in the populations across the globe and also the leading cause of hospitalisations in adults over 65 years of age[1]. Based on disease specific estimates of prevalence and incidence rates of heart failure, the prevalence of heart failure in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease range from 1.3 to 4.6 million, with an annual incidence of 0.5 to 1.8 million.[3] Unlike western countries where heart failure is predominantly a disease of elderly, in India it affects younger age groups. The double burden of rising cardiovascular risk factors and persistent 'pre-transition diseases' such as rheumatic heart disease, limited health infrastructures and social disparities contribute to these estimates[4].

Despite great advances in medical management, the prognosis remains poor. Heart failure can be disabling

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and it can severely reduce a patient's quality of life. The readmission rates of patients with heart failure within three to six months after hospital discharge has been reported to range from 17 to 55% depending on the age and heart failure stage[5].

Pro-B type natriuretic peptide is a neurohormone which is stored mainly in the myocytes of the ventricle and released as a result of pressure and volume overload or myocardial damage. Pro-BNP is synthesised as an inactive pro hormone that is split into an active hormone BNP (32 amino acids) and an inactive amino terminal fragment, N-Terminalpro BNP(76 amino acids)[6,7]. NT Pro-BNP has longer half life than BNP and is less influenced from acute therapeutic regimes and clinical deteriorations which make it suitable for predicting cardiac functions[8].

BNP and NT pro- BNP have shown to be strong predictor of morbidity and mortality[9].More over the BNP levels have been reported to be strong independent predictors of early re admission or death due to HF, and are more useful than clinical or echocardiographic parameters during acute care[10].

In India, particularly rural India, there is a lack of infrastructure like echocardiography gadgets and shortage of cardiologists and echotechnicians to interpret the echocardiographic images[4]. So diagnosis and risk stratification of heart failure patients for management is difficult. This study aims to evaluate the use of NT-proBNP level estimation for making diagnosis, predicting cardiac events , morbidity and mortality in heart failure, which neither needs the echocardiography gadgets nor a skilled echotechnician/cardiologist to interpret.

AIMS AND OBJECTIVES

- To look for the correlation between NT-proBNP levels and the NYHA classes of heart failure.
- To find the relation of left ventricular ejection fraction to the levels of NT-proBNP in patients with congestive heart failure.
- To assess the prognostic value of NT-proBNP levels as an indicator of hospital outcome in patients with heart failure.
- To determine the cut off value of the NT-proBNP for the prediction of adverse hospital outcome in patients with CHF.

MATERIALS AND METHODS

This study was hospital based prospective study,undertaken in 35 patients admitted in the Post Graduate Department of Medicine and the Department of cardiology at M.K.C.G Medical College and Hospital, Berhampur, Odisha with features of congestive heart failure from 2014 February to 2015 October.

Patients having clinical evidence of congestive heart failure according to Framinghams criteria[2] and confirmed by 2D echocardiography based on the European Society of Cardiology Guidelines for diagnosis of heart failure[11] were included in the study.

Patients with abnormal renal function tests,obesity,anaemia,chronic liver disease,sepsis and patients who required admission in the ICU were excluded from the study.

Appropriate investigations like blood routine examination, urine routine examination, renal function tests, liver function tests, cardiac troponin I (in selected cases), chest X ray, electrocardiogram and 2D echocardiogram were done in the hospital. The plasma levels of NT-proBNP were serially determined on the admission day and on the seventh post admission day. The clinical status of the patients were assessed daily with clinical examinations and necessary investigations till their discharge or in-hospital death.

NT-proBNP concentration was measured by Enzyme-linked fluorescent Assay (VIDAS Automated quantitative test). The analytical range was 20-25000pg/ml. The recommended decision thresholds as per the manufacturer (Bio Merieux, France) literature were 125pg/

ml for patients <75 years old and 450pg/ml for patients e"75 years old.The assay principle combines a one step immune assay sandwich method with a final fluorescent detection (ELFA).

In the study all patients were subjected to M-mode as well as colour Doppler echocardiography. It was performed with the use of a wide angle rotator mechanical sector scanner with 3.5 MHz transducer tall tracing recorded at the tip of the mitral valve.

This study was carried out in accordance with the principles approved by the ethics committee of MKCG Medical College, Berhampur. Written informed consent was obtained from every patient in the study.

Statistical analysis was performed with the SPSSS software package (version 21.0; SPSS, Inc. Chicago, IL, USA). Receiver operating characteristic (ROC) curves were drawn to quantify the ability of NT-proBNP to predict outcome at the admission and the seventh post admission day.

OBSERVATIONS

Table:1-Baseline characteristics of patients with CHF

Parameters	Values
Age(years)	55
Male :female	1.7:1 (62.86%:37.14%)
Height(cm)	161.14
Weight(kg)	59.4
BMI(kg/m^2)	22.62
Hb(gm/dl)	13.32
HR(/min)	86
SBP(mm of Hg)	114.66
DBP(mm of Hg)	73.83
S.creatinine(mg/dl)	1.31
LVEF(%)	31.8
Duration of Hospitalisation (days)	9

Table:2-Baseline clinical parameters of patients with CHF

Parameters	No of cases	% of cases
Oedema	30	85
Orthopnea	13	37.14
PND	13	37.14
raised JVP	20	57.14
B/L basal crepitations	35	100
S_3	10	28.57
Cardiomegaly	11	31.43

In the study 25.71%(9) of the patients CHF had hypertension and 17.14% (6) of the patients had diabetes mellitus .Out of the total 35 cases, 22.86% had ischemic heart disease and 17.14% had rheumatic heart disease.37.14% of patients had dilated cardiomyopathy. 17.14% had hypertensive heart disease. 2.86% had congenital heart disease and for 2.86% of the patients cause of heart failure could not be identified.

Table:3-NYHA class distribution in cases of CHF

NYHA CLASS	No	%
I	3	8.6
II	18	51.4
III	11	31.4
IV	3	8.6
total	35	100

The mean NT-proBNP level of patients with CHF on the admission day was observed to be 4784±1905pg/ml. The mean NT-proBNP level on the seventh post admission day was found to be 2722±1652 pg/ml. The mean NT-proBNP level on the admission day was found significantly higher than the seventh day values. (p=0.0001)

In the study, a total of 35 cases of CHF were included and followed up during the course of their hospital stay. At the end of the same hospitalisation they were

classified as those with adverse outcome and favourable outcome based on the presence or absence of any new onset arrhythmias, improvement or deterioration of NYHA functional class and death. Out of the total 35 cases of CHF,28 patients (80%) had a favourable outcome at the end of hospital stay(i.e. improvement of NYHA functional class or absence of any new onset arrhythmias or death).7 patients (20%) had an adverse outcome at the end of the hospital stay(i.e. deterioration of NYHA functional class or presence of new onset arrhythmias or death).Out of the 7 patients with adverse hospital outcome, 57.14% expired during their hospital stay, 42.86% had deterioration of NYHA functional class and none had any new onset arrhythmias.

Of the patients with the favourable outcome, maximum patients belonged to NYHA class II (60.71%). NYHA class I and III comprised of 10.71% and 28.57% of the patients with favourable outcome. There were no patients of NYHA class IV in this group.Of the patients with the adverse hospital outcome, maximum patients belonged to NYHA class III and IV (42.86% each).14.29% of the patients with adverse outcome was in NYHA class II.Statistically significant difference was observed between the various NYHA classes with respect to favourable and adverse hospital outcome(p=0.003).

The mean LVEF of cases with the favourable and adverse hospital outcomes were 33.79% and 23.86% respectively. The observed difference between the two groups was statistically significant with p value of 0.0001. Mean duration of hospital stay in patients with the favourable and adverse outcome in this study were 8 and 12 days respectively, with statistically significant difference between the two groups. ($p<0.001$).

The mean NT-proBNP levels at the admission day and at the seventh day of hospitalisation for the cases with favourable hospital outcome is 4158.43±282.2 pg/ml and 2118±192.9 pg/ml respectively. The observed difference between them were statistically significant with p value of 0.001.

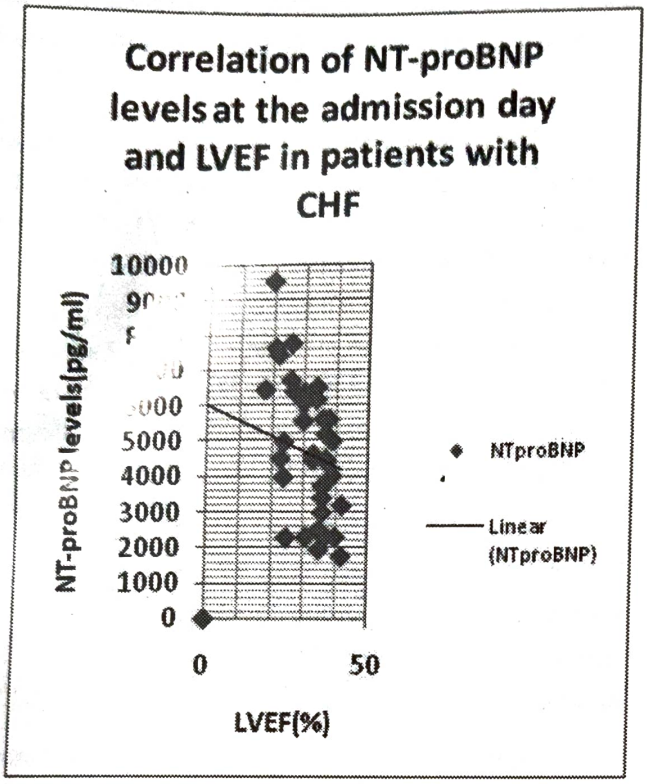
For patients with adverse hospital outcome, the mean NT-proBNP values at the admission day and at the seventh day of hospitalisation were 7284.71±468.5 pg/ml and 5539±368pg/ml respectively. The observed differences between them were statistically significant with p value of 0.0191.The comparison of mean NT-proBNP in patients with the favourable and adverse hospital outcome both during admission and at the seventh day was statistically significant with p value of 0.001 for both of them.

Mean NT-proBNP levels of NYHA class I,II,III and IV are 2950.67,4578.61,5215.82 and 6262.67 pg/ml respectively. There is strong correlation between NYHA classes I and II; and III and IV with the mean NT-proBNP levels with $r=0.7983$, $p<0.0001$ and $r=0.9366$, $p<0.0001$.

Mean NT-proBNP values of patients with favourable outcome in NYHA class I and II were 2950.67 and 4578.61 pg/ml respectively. There were no patients in NYHA class I and II with adverse outcome. Mean NT-proBNP levels of NYHA class III with favourable and adverse hospital outcome were3595.57 and 8051.25pg/ml respectively. All NYHA class IV patients had an adverse outcome with mean NT-proBNP level of 6262.67 pg/ml.A strong positive correlation is observed between mean NT-proBNP levels of NYHA class III of CHF with hospital outcome with correlation coefficient of 0.505.

Mean NT-proBNP level in the patients with CHF was 4783.68pg/ml and mean LVEF was 31.8%.It was observed that NT-proBNP levels and LVEF is inversely correlated with a correlation coefficient of -0.592.the observed correlation was statistically significant with p value of 0.0002.On the whole in patients with CHF who had high NT-proBNP levels, LVEF was found to be significantly low.

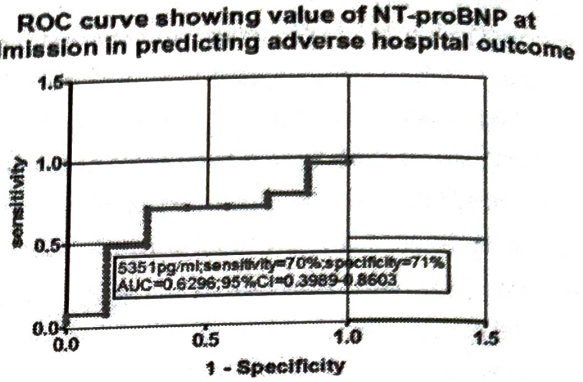
Graph:1



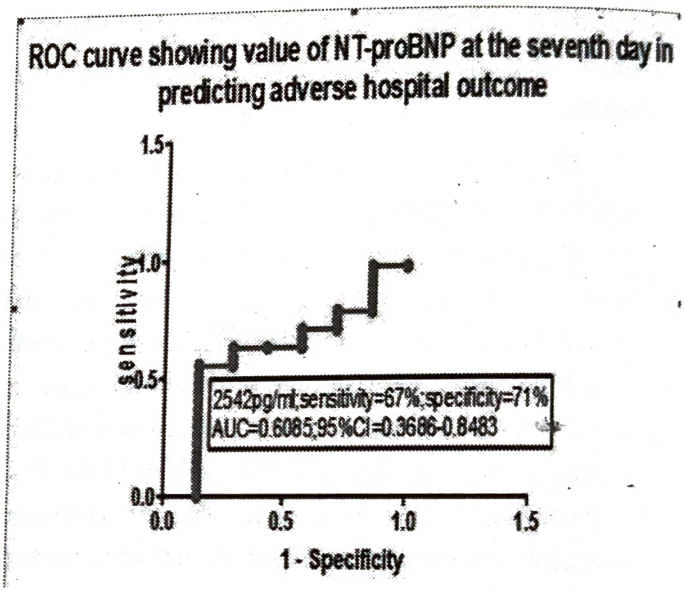
The mean NT-proBNP level at the admission day in patients of CHF was 4783.68pg/ml. The average duration of hospital in the study subjects was 12 days. A positive correlation was observed between NT-proBNP levels at the admission day and duration of hospital stay of the patients with CHF with pearson correlation coefficient(r)=0.683 which was statistically significant with p value of 0.000.

The receiver-operating characteristic curve showed that the threshold value of NT-proBNP at admission having the highest sensitivity and specificity (70% and 71% respectively) for predicting adverse hospital outcome was 5351 pg/ml.The ROC curve showed that the threshold value of NT-proBNP at the seventh day of admission having the highest sensitivity and specificity(62% and 71% respectively) for predicting the adverse hospital outcome was 2542 pg/ml.

Graph:2



Graph:3



DISCUSSION

All patients of CHF were evaluated with NT-proBNP level at the admission day and the seventh post admission day. The mean NT-proBNP level of patients with CHF on the admission day was 4784±1905pg/ml. The mean NT-proBNP level on the seventh post admission day was 2722±1652 pg/ml. The mean NT-proBNP level of patients with CHF on the admission day was found significantly higher than the seventh day values (p=0.0001).

Di Somma and colleagues[12] has demonstrated a rapid decline of NT-proBNP in response to therapy in HF

patients. *Bayés-Genís and colleagues*[13] examined the prognostic value of the percentage decrease of NT-proBNP during the course of hospitalization in patients with HF. In that study, after 48 hours with effective treatment NT-proBNP steadily decreased in patients with ADHF.

Statistically significant association was observed between the various NYHA classes with respect to favourable and adverse hospital outcome (p=0.003).A strong association between NYHA class and outcomes in patients with systolic heart failure has been consistently reported by several studies by Scrutinio et al, Madsen BK,etc

According to *Marcus Noveanu et al*,[14] NT-proBNP levels were higher in patients with heart failure who died or experienced cardiovascular events. In patients with a favorable outcome, NT-proBNP levels decreased during the course of hospitalization, In the study by *Paulo Bettencour et at*[15] the median admission NT-proBNP level was 6778.5 pg/mL and 4137 pg/ml at admission day and at 1 week of post admission.

Statistically significant difference was observed between NT-proBNP levels of the various NYHA classes with respect to favourable and adverse hospital outcome(p=0.003). A strong positive correlation is observed in this study between mean NT-proBNP levels of NYHA class III of patients with favourable and adverse hospital outcomes with correlation coefficient of 0.505.This observation in our study points that NT-proBNP is strongly related to the hospital outcome in patients with heart failure in various NYHA class of the patient.

Januzzi et al[16] demonstrated the significant relationship between NYHA symptom severity and NT-proBNP levels; as symptom severity rose, a significant increase in median NT-proBNP levels was observed (*P*=0.008), although significant overlap existed between the NYHA groups. According to *Adil Hussein Alhassannay et al* in 2013[17] ,NT-proBNP levels correlates best with NYHA classes III and IV and inconsistent correlation were obtained between NYHA classes I and II. Studies conducted *by Zhu Y,Chai B,Wang LL et al*[18] in 2008 in department of cardiology, Sichuan University, China investigated the diagnostic value of NT-proBNP in 106 patients with cardiac dyspnea. A significant difference was observed in different NYHAclasses [NYHA II (862.76±818.46)pg/ml, NYHA III (2444.75±556.61) pg/ml, NYHA IV (7574.60±3721.39) pg/ml,p<0.05]

Mean NT-proBNP level of the patients with CHF was 4783.68pg/ml and mean LVEF was 31.8%.It was observed that NT-proBNP levels and LVEF is inversely correlated with a correlation coefficient of -0.592.The observed correlation in the study was statistically significant with p value of 0.0002.On the whole in patients with CHF, as the LVEF decreases, the NT-proBNP levels tend to increase. This observation in the study precisely points towards the capability of NT-proBNP level to correlate with the LVEF of the patient.

Jannuzi et al[19] demonstrated modest, but significant, relationship existed between ventricular function and natriuretic peptide concentrations in patients with heart failure. (*r*="0.289,*P*<0.001). Studies conducted *by Zhu Y,Chai B,Wang LL et al*[18] in 2008 in department of cardiology, Sichuan University, China investigated the diagnostic value of NT-proBNP in 106 patients with cardiac dyspnea and found out that the concentration of NT-proBNP had a negative correlation with LVEF(r=-o.812).

A positive correlation was observed between NT-proBNP levels at the admission day and duration of hospital stay with Pearson correlation coefficient(r) =0.683 which was statistically significant with p value of 0.0006.In the whole, patients with high NT-proBNP levels had a longer duration of hospital stay in our study.

In the *BASEL study* by *Boldanova T et* al[19], NT-proBNP level testing was associated with the median time of discharge at 11 days. In *the IMPROVE-CHF study*[20],NT-proBNP had no significant relation to the length of hospital stay.In this regard, findings of our study are more comparable with the BASEL study than the IMPROVE-CHF study. This difference is probably due to difference

in the hospital care and the varied aetiology of heart failure requiring different periods of hospital stay.

The receiver-operating characteristic curve showed that the threshold value of NT-proBNP at the admission day having the highest sensitivity and specificity (70% and 71% respectively) for predicting adverse hospital outcome was 5351 pg/ml.The receiver-operating characteristic curve showed that the threshold value of NT-proBNP at the seventh day of admission having the highest sensitivity and specificity(62% and 71% respectively) for predicting adverse hospital outcome was 2542 pg/ml.Out of the two values, NT-proBNP levels at admission has more prognostic and predictive value since it has more specificity and sensitivity compared to the seventh day values.

In *the ICON* study, *Jannuzi et al* 2006[19] sought to evaluate the utility of NT-proBNP as a short term prognostic indicator in patients with heart failure. In the study, multivariate analysis determined NT-proBNP levels above 5180pg/ml to the strongest independent predictor of mortality and adverse outcome in patients with heart failure. In *PRIDE* Study by *Januzzi et al*[21],showed the threshold values at which NT-proBNP had sensitivity(83%) and specificity(76%) was 4850pg/ml.

Conclusion

This study establishes the role of NT-proBNP as a prognostic marker of hospital outcome in patients with congestive heart failure. This also demonstrated a steady correlation of NT-proBNP levels with both NYHA class and left ventricular ejection fraction in patients with heart failure. The admission NT-proBNP was not only useful for diagnosis, but also strongly predicted likelihood for adverse hospital outcome in hospitalised patients with heart failure with more sensitivity and specificity than the seventh day NT-proBNP. The optimal cut off point of NT-proBNP levels for predicting hospital outcome was found to be 5351pg/ml done at the admission day. The cut-off point for NT-proBNP will help clinicians more confidently utilize NT-proBNP in the evaluation of the heart failure patients, preserving sensitivity for younger patients with suspected HF, while optimizing specificity for elderly patients. Timely prognostic information by NT-proBNP measurements at the admission day may also allow clinicians to individualise and intensify treatment in hospitalised patients at a very early stage of hospitalization and thus improve prognosis.

However because of the modest sample size and the exclusion of the critically ill patients, further research is needed to define optimum cut off values of NT-proBNP levels. It should preferably be a longitudinal study with a much larger sample size and longer term follow up.

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Original article

CLINICO-EPIDEMIOLOGICAL PROFILE OF TUBERCULOSIS IN HIV INFECTED PATIENTS

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ABSTRACT

Introduction: HIV-TB co-infection is a major challenge faced by the healthcare system in our country. Tuberculosis infection in the already immunocompromised host can present with wide variety of clinical symptoms, some of them difficult to identify and also leads to high mortality.

Material: This is an observational study in which all consecutive adult patients attending a tertiary care hospital for a period of one year with HIV-TB co infection are enrolled. There were 231 patients. The clinical parameters are studied after a detailed history and clinical examination. The diagnosis of Tuberculosis was made by relevant investigations like Sputum AFB, Chest X-ray, CSF Study, CT Scan, Pleural Fluid Study, Ascitic fluid study etc. Then the results were compiled.

Observations: Majority of the patients were males-191(82.68%), females-38(16.45%) & TGTS-2(0.87%). Age group mostly affected were 26-35 years(38.1%) and 36-45 years(38.1%). Extrapulmonary TB constituted 56.28% and Pulmonary TB-43.72%. 41.99% completed anti-TB treatment and mortality was 12.99%. Mean CD4 count at the time of TB diagnosis-218; and patients with low CD4 count at the time of diagnosis had high mortality.

Conclusions: Extrapulmonary TB is predominant among HIV TB coinfection and the working class population is affected more than the rest. TB Meningitis and Disseminated TB are associated with a bad prognosis when compared to other forms of TB. A low CD4 count at the time of Tuberculosis diagnosis is associated with a higher mortality.Early suspicion diagnosis of tuberculosis and prompt institution of ATT in HIV patients reduces mortality and morbidity significantly.

INTRODUCTION

Tuberculosis is a disease which decided the fate of many generations and still continues to create everlasting dilemmas in the lives of millions in many parts of the world especially the underserved countries of Asia and Africa. The history of tuberculosis has two major landmarks, the discovery of anti-tubercular drugs and the outset of AIDS; both had immense influence on the disease management. A combination of the two deadly diseases TB and HIV continues to be a stumbling block faced by almost all the physicians of the nation. The behaviour of this combination is of high scientific interest and the ways each disease abetting the other has undergone many national and international studies. The

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resurgence of tuberculosis in western countries due to HIV/AIDS is also being contributing significantly for the disease burden on the globe. The latest estimates included in this report are that there were 9.6 million new TB cases in 2014 (1.1 million-13% HIV positive) and 1.2 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people).

People living with HIV are 29 times more likely to develop TB disease than those who are HIV-negative.[1] The number of people dying from HIV-associated TB has continued to fall globally, from a best estimate (and peak) of 540000 in 2004 to 360000 in 2014 (with approximately equal numbers of deaths among men and women). Although curable, tuberculosis is estimated to be the single largest cause of death among AIDS patients globally, being responsible for at least 12% – and perhaps up to 30–50% – of all AIDS-related deaths that have occurred[2]. At the individual patient level, TB and HIV form a type of "disease complex," with each pathogen manipulating the host response in such a way as to enhance the other pathogen's ability to cause disease pathology. In most cases, mycobacterium is the first pathogen to infect the patient, with HIV infection occurring later. With progressive HIV infection and its associated immune compromise, there is an enhanced risk of reactivation of latent TB infection (LTBI), an increased likelihood of progressive TB disease from newly acquired TB infection, and an increase in recurrent TB or TB relapse. In the cases where HIV infection predates TB infection – such as in mother-to-child transmission of HIV – the generalized immune stimulation that accompanies secondary TB infection results in driving HIV replication and disease progression.[3]

This study describes the clinical and epidemiological features of HIV-TB co infected patients presented in our hospital.

MATERIALS AND METHODS

Patients were selected among those attending the General Medicine outpatient department and respective inpatient wards between March 2014 and February 2015. Further data were collected from the ART center of MKCG Medical College, Brahmapur. All HIV positive patients were screened for tuberculosis. Those patients with a strong suspicion of HIV/AIDS infection, were subjected to screening tests for anti-HIV antibodies after pre-test counselling and informed consent.

A detailed clinical history and complete general physical and systemic examination findings of HIV/TB patients were recorded. All the routine investigations were done.

Two simple rapid immunobinding assays were selected for the HIV serological testing. It was done in the ICTC center of our institute. The approach was consistent with WHO recommendations.

The diagnosis of tuberculosis was based on the WHO case definition of tuberculosis, according to disease type or pulmonary smear status. All the pulmonary TB suspects were sent to make a sputum smear examination at the RNTCP accredited laboratory in our college. All extrapulmonary cases were examined individually.

All suspect cases of pulmonary TB gave two sputum specimens to the RNTCP lab. Sputum Negative cases were considered as TB when the chest x ray showed changes consistent with tuberculosis.

RESULTS

During the period of study 231 patients qualified to be enrolled. 191(82.68%) were males and 38(16.45%) were females. 2 were transgender/transsexuals. The age distribution of the patients are shown below.

Age	No. of Patients	Percentage (%)
15-25	23	9.95
26-35	88	38.1
36-45	88	38.1
46-55	26	11.26
56-65	4	1.73
>65	2	0.86

Most of the patients were manual labourers (81=35.06% unemployed (36=15.58%); Semi skilled wr 12.12%); self-employed (23=9.96%); House w (23=9.96); Local transport worker (11=4.76%); skilled worker (7=3.03%); Service (6= 2.6%) ; truck driver (5=2.16%); Hotel staff (4=1.73%); Student (3=1.3%); Agricultural land owner (3=1.3%); retired (1=0.43%).

141(64.04%) patients were found alcoholic; 120(51.95%) patients were tobacco users, 68(29.44%) were smokers; 69(29.87%) were having no addictions.

Number of married individuals = 178(77.06%); unmarried =32(13.85%); Divorced/ widowed = 21(9.09%).

Out of the 178 married persons in the study group 85(47.75%) individuals had a HIV positive partner while 58(32.58%) had a HIV negative partner. 35(19.66%) of them are not aware of their partners HIV status.

Most of the patients (226 = 97.845) are heterosexuals while only 5(2.16%) are homosexuals and all of them were males.

Out of the 231 cases 101(43.72%) were Pulmonary tuberculosis and 130(56.28%) were extrapulmonary tuberculosis.

During the study period 101 patients had pulmonary TB; 55(54.46%) patients were sputum positive for AFB and 46(45.54%) were sputum negative.

Pleural TB (50 = 38.46%) was the most common type of extrapulmonary TB in our study group. It was followed by lymph node TB (36 = 27.69%) and gastrointestinal TB (21 =16.15%). 12(9.23%) patients had meningeal TB and 5(3.85%) had multiple sites of involvement. There were 2(1.54%) cases of skin TB and tuberculoma each. One case (0.77%) each of pericardial TB and skeletal TB was included in the study.

Most of the patients with PTB complained of cough (87=86.14%). Weight loss (62=61.39%) and loss of appetite (45=44.55%) were also frequently observed. Fever was seen 36(35.64%) patients. 11(10.89%) complained of fatigue. 1(0.99%) had hemoptysis and another had abdominal distension.

Most of the patients with EPTB had fever, weight loss and loss of appetite. Abdominal distension and diarrhea were the major symptoms in gastrointestinal TB, while cough and chest pain were the major symptoms in pleural TB. Neck was the commonest site for TB lymphadenitis. Most of the patients with TB meningitis presented with altered sensorium.

The CD4 count of the patients at the time diagnosis of TB is given in the following table.(mean CD4 count=218cells/mm3)

CD 4 Count	No: of Patients	Percentage(%)
<=50	19	8.23
51-100	49	21.21
101-150	41	17.75
151-200	33	14.29
201-250	19	8.23
251-300	15	6.49
301-350	19	8.23
351-400	7	3.03
401-450	9	3.90
451-500	4	1.73
>500	16	6.93

Out of the 101 cases of PTB in our study, 52(51.49%) patients had infiltrations in their chest x-ray. 21(20.79%) had fluffy shadows and 11(10.89%) had non homogenous patches. Miliary shadows were present in 10(9.9%) cases. 4(3.96%) cases had consolidation and 2(1.98%) had cavity. One (0.99%) chest x-ray had bronchiectatic changes and another one had an isodense shadow.

Most of the patients with Pulmonary TB(60=59.41%) weighed between 41-50kgs. 24(23.76%) patients weighed 31-40kgs; 12 (11.88%) patients weighed 51-60kgs; 2(1.98%) patients were less than 30kgs. 2(1.98%) were between 61-70kgs. There was one (0.99%) patient who weighed more than 90kgs. The mean weight = 44.9 kg; mean BMI = 17.46kg/m^2.

Anemia was a common finding and the mean Hb was 8.6 g/dL.

Majority of the patients (199 = 86.15%) were started on CAT 1 ATT. 21(9.09%) patients had CAT 2 ATT. 3(1.3%) patients were having MDR TB so started in with CAT 4 DOTS. 8(3.46%) patients had taken non DOTS therapy.

Out of the 231 patients in our study 97(41.99%) were declared TB cured after treatment. Another 97(41.99%) patients are continuing the treatment. 30(12.99%) patients died and 7(3.03%) were lost to follow up.

Discussion

Our study which was conducted for a period of one year revealed that the disease burden of tuberculosis is substantial among the HIV affected population. Tuberculosis still marks as the leading cause of mortality and morbidity among the PLHA group. Total number of patients enrolled in our study was 231 which included all the patients who came to the ART centre of our hospital and the general medicine wards for a period of one year. During the same period of time 971 new cases of HIV were registered in the ART centre of our institute. Among them 136 individuals contracted tuberculosis during the study period.

Among the 231 patients 191 (82.68%) were males and 38 (16.45%) were females. 2 (0.87%) revealed themselves as transsexuals. This shows a clear preponderance of male population in the disease cohort. Studies done by Jiang et al in mainland of China also showed a clear male majority[4] in HIV-TB coinfection. Those studies done in RIMS Manipur by Devi et al[5]and Khosravi et al[6] in Iran also showed that males are more affected. But a study by Sawant SS et al[7] in Mumbai showed a marginal female majority as large number of female sex workers were included in that study.

The high prevalence of HIV in males in our study must be due to the high rate of migration of the youth to other states in search of job opportunities where they are exposed to high risk activities. The main regions of migration include Surat in Gujarat, Mumbai, Chennai and Kerala.[8] Another reason for the large male to female disparity may be because the females are often neglected and deprived of health care facilities resulting in an underestimation of their numbers.

The mean age of patients in our study was 37 years and the range was from 15 years to 70 years. The major age groups were 26-35 & 36-45 years which comprised of 76.2% (38.1% each) of the study population. This clearly shows that the working population of the society is affected more than the rest as they are more sexually active and also have more chances for exposure to TB infection. This is consistent with the study done by Sawant et al in Mumbai[7] and Kumar et al[9] in Delhi. 26 patients, (11.26%) were between 46-55 years and 23(9.95%) were between 15 and 25 years. Only six patients were above 56 years

of age. The decrease in number of elderly population is may be due to the high mortality of the HIV patients in the region.

Majority of the participants are manual labourers (81=35.06%) working either in their native place or in the above mentioned high risk migrant areas. This is consistent with the study done by Kumar et al in Delhi which had 38.1% of manual labourers[9]. The dwelling areas of the labourers are congested and are often deprived of adequate ventilation or hygiene which make them prone to infections especially tuberculosis.

Substance abuse and addictions play a major role in the HIV transmission. Most of the unsafe activities which culminate in disease transmission are done under the influence of alcohol or cannabis.141 patients (61.04%) gave history of alcohol abuse in our study. Alcohol use causes disinhibition and diminished perception of risk, which increase the likelihood that a person would put him or herself (or his/her partner) at risk for HIV infection by engaging in unsafe sexual practices, such as having multiple sex partners, unprotected intercourse, sex with high risk partners (e.g., injection drug users, commercial sex workers), and exchanging sex for money or drugs. There is a three-fold risk increase of active TB associated with consumption of more than 40 g alcohol per day, and/ or having an alcohol use disorder. This could be due to both increased risk of infection related to specific social mixing patterns associated with alcohol use, as well as influence on the immune system of alcohol itself and of alcohol related conditions.[10]

77.06% of the patients were married while 13.85% were unmarried. This is contrary to many other studies especially those done outside India and may be due to the social & cultural difference. 9.09% patients were single due to various reasons like death of the partner, divorce etc. The affected husbands are the viral source for most of the village women[11]

Out of the 231 patients with HIV-TB coinfection included, 101(43.72%) patients suffered from Pulmonary TB. The rest 130 patients were diagnosed to have extrapulmonary TB (56.28%). This clearly shows that EPTB is more common than pulmonary TB in HIV- TB co infection. This can be compared with 54.4% of pulmonary TB and 45.6% of EPTB shown in studies done by Kumar et al[9]. A study in Thailand had 70% pulmonary and 30% extrapulmonary disease. Among HIV-infected patients with TB, extrapulmonary disease are more common, particularly in those with advanced immune suppression.[12] This fact can explain the increased number of EPTB cases in our study population as many patients are detected HIV positive at very late stage of the disease.

Out of the 101 pulmonary TB cases in our study, 55(54.46%) were positive for sputum AFB and the rest 46(45.54%) were negative. This apparent predominance of smear negative disease may be partly due to 1) heavy workloads increasing the likelihood of false-negative laboratory errors, and 2) misdiagnosis of other HIV-related pulmonary conditions as smear-negative TB, but several studies have found that smear-negative disease is actually more common among HIV-positive patients.[13] The level of immunosuppression among the HIV-positive patients in the various studies may also have differed. Less severely immunocompromised HIV-positive patients tend to have classic cavitary TB which is smear-positive. As the level of immunity decreases with advancing HIV disease, atypical pulmonary features predominate and smear examinations prove less sensitive.

The relationship between CD4 count and Tuberculosis is considered very important as the decline in the level of immunity is considered as a major risk for acquisition and reactivation of infections. In our study, 49(21.21%) patients were having a CD4 count between 51-100 at the time of diagnosis of TB. 41(17.75%) patients were in the 101-150 group and 33(14.29%) patients in the 151-200

group. 19(8.23%) patients had less than 50 CD4 cells/mm3. Another two groups of 19(8.23%) patients each had CD4 count between 210-250 and 301-350. 16(6.93%) patients had CD4 count more than 500. 15(6.49%) had it between 251-300, 9(3.9%) between 401-450, 7(3.03%) between 351-400 and 4(1.73%) between 451-500. The mean CD4 count of patients having HIV-TB coinfection was 218 cells/mm3. It ranged from 21-1044 cells/mm3. It is slightly higher than what Kamath et al had derived from his studies (mean=174).[14] It was even less in studies done in Shimla (mean = 123)[15] and in AIIMS, New Delhi (mean = 120).[16] But in a Brazilian study the CD4 counts were better than ours (mean = 307; range = 6-1531).[17]

Our study concluded that in the selected population the risk of Tuberculosis increases remarkably when the CD4 count falls below 200 cells/mm^3. (61.5% of the patients had a CD4 count <=200). The highest number of TB cases were recorded when the CD4 count was between 51 to 100(21.21%). Though there is a decline in the number of cases as the CD4 count increases, TB is prevalent in all groups. In the study done by Perisseet al[18] 78.4% of patients of HIV-TB coinfection were having CD4 count <=200cells/mm3. The study done by Jaryal et al in Shimla[15] had 81.6% of patients with CD4 count less than 200cells/mm3. This contrary data suggest that our study population acquire TB infection even if the CD4 count higher may be because of higher prevalence of TB in general population in this part of the state.

Majority of the patients (199 = 86.15%) were started on CAT 1 ATT. 21(9.09%) patients had CAT 2 ATT. 3(1.3%) patients were having MDR TB so started in with CAT 4 DOTS. 8(3.46%) patients had taken non DOTS therapy. Out of the 231 patients in our study 97(41.99%) were declared TB cured after treatment. Another 97(41.99%) patients are continuing the treatment. 30(12.99%) patients died and 7(3.03%) were lost to follow up. This is compared with study done by Kamath et al[14] in Karnataka with a cure rate of 75.6%; death - 11.78%; lost follow up – 3.12% & 9.49% of patients continuing treatment. Low number of cured patients in our study may be because of the large number of patients continuing the treatment. Study group of Shastri et al had a death rate of 15.7%.[19]

CONCLUSION

HIV- TB co infection is a major healthcare issue in this part of the country. It most commonly affects the younger economically productive section of the society. Early suspicion diagnosis of tuberculosis and prompt institution of ATT in HIV patients reduces mortality and morbidity significantly. Therefore, adequate knowledge of the manifestations of tuberculosis in HIV-infected patients is absolutely necessary for optimal management and to reduce mortality and morbidity.

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Review article

THYROID DYSFUNCTION DURING PREGNANCY-AN OVERVIEW

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INTRODUCTION

The thyroid physiology changes during pregnancy to cope up with the increased metabolic demand [1]. Around 1-2% of pregnant women are affected by thyroid disorders. During pregnancy production of thyroxine (T_4) and triiodothyronine (T_3) increases by 50%, along with a 50% increase in the daily iodine requirement. Also there is increase renal clearance of iodine and transfer of iodine to fetus. At least 250µg/day of iodine intake is required to meet the demand. The gland increases 10% in size during pregnancy in iodine-replete areas and by 20%–40% in areas of iodine deficiency. These physiological changes may result in hypothyroidism in the later stages of pregnancy in iodine-deficient women who were euthyroid in the first trimester. The placental human chorionic gonadotropin (hCG) has a structural homology to TSH as both have identical alpha subunit. It directly stimulates the thyrocytes and has thyroid growth-promoting activity. HCG levels peak at 8-10 weeks of pregnancy. HCG induces a physiological blunting of pituitary-thyroid axis leading to suppressed TSH level with lowest level in first trimester[2]. There is a reduction in the Th1 cell mediated immunity and antibody production (TPO-Ab,Tg-Ab,TRAbs) causing remission of many autoimmune diseases including Graves' disease and Hashimoto's thyroiditis during pregnancy. During post partum period these antibodies rise to prepregnancy level. Approximately 33–50% of women who are positive for TPO or Tg antibody in the first trimester may develop postpartum thyroiditis.

Thyroid function tests during pregnancy

Following conception , thyroxine binding globulin (TBG) concentrations increase by 6–8 weeks mainly due to increase oestrogen level and remain high until delivery. Thyrotropic activity of hCG results in a decrease in serum TSH in the first trimester. Thyroid function test results of healthy pregnant women differ from those of healthy non pregnant women and this calls for trimester-specific reference interval[3]. FT4 level decreases with progress of pregnancy.The most widely applied tests are TSH and free T_4 levels .The recommended trimester-specific reference ranges for TSH are: 1st trimester, 0.1–2.5 mIU/L; 2nd trimester, 0.2–3.0 mIU/L; 3rd trimester, 0.3–3.0 mIU/L. Isolated hypothyroxinemia is defined as a normal maternal TSH concentration in conjunction with FT_4 concentrations in the lower 5th or 10th percentile of the reference range.

Hypothyroidism in Pregnancy

In India the prevalence of hypothyroidism is 4.8-14% with most of the cases being subclinical[4]. Overt hypothyroidism (OH) is defined as an increase in serum TSH (usually >10 mIU/L) associated with a decreased concentration of thyroxine. On the other hand, subclinical

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hypothyroidism(SCH) is defined as increase in serum TSH (usually 4-10 mIU/L) associated with normal serum T4 and T3. The prevalence is higher in areas of iodine insufficiency. The iodine deficiency may be due to consumption of cruciferous vegetables, soy and millets, cigarette smoking, deficiency of selenium, iron and vitamin-A. In iodine sufficient areas, the most frequent cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis). Thyroid auto-antibodies were detected in <50% of pregnant women with SCH and in more than 80% with OH. Other causes of maternal hypothyroidism are thyroidectomy, radio ablation of the gland, external irradiation and drug effects. Secondary causes like pituitary disease and hypothalamic disease should be ruled out.

Adverse outcomes associated with Hypothyroidism in pregnancy

As fetus depends on maternal supply of thyroid hormone in 1st trimester, untreated hypothyroidism during pregnancy can have detrimental effects upon fetal neurocognitive development[5]. Studies confirmed reduction in intelligence quotient (IQ) among children born to untreated hypothyroid women when compared with euthyroid controls. There is increased risk of premature birth, low birth weight, and 60% chance of fetal loss [6]. There is maternal risk of eclampsia, preeclampsia, gestational hypertension , placental abruption and PPH.

SCH is associated with an increased risk of adverse pregnancy complications and possibly with an increased risk of neurocognitive deficits in the developing fetus[7]. SCH increases the risk of pregnancy complications in anti-thyroid peroxidase antibody positive (TPOAb+) women.

MANAGEMENT

Treated hypothyroid patients receiving levo-thyroxine(LT_4) who are planning pregnancy should have their dose adjusted in order to optimize serum TSH values to <2.5 mIU/L preconception.Maternal hypothyroidism should be avoided by early diagnosis at the first prenatal visit or at the time of diagnosis of pregnancy[8].

The requirement for T_4 (or exogenous LT_4) increases as early as 4–6 weeks of pregnancy and then gradually increases up to 16–20 weeks to become plateau thereafter until the time of delivery[9]. In known hypothyroidism, serum hCG and TSH cannot stimulate T_4 production during pregnancy. Those patients who are already on thyroid hormone supplementation prior to pregnancy need dose escalation of 30-50%[10]. Dose increment will be greater in patients without functional thyroid tissue (e.g., due to radioiodine ablation, total thyroidectomy) than in those with residual thyroid tissue (Hashimoto's thyroiditis).

In patients diagnosed with overt hypothyroidism during pregnancy, therapy should be started with full replacement dose of LT4 (1.6-2.0 µg/kg/d) to normalize thyroid function tests as rapidly as possible.

Normalization of TSH levels throughout gestation is the goal.TSH levels should be maintained as follows- 1st trimester: 0.1-2.5mU/L, 2nd trimester: 0.2 - 3.0mU/L, 3rd trimester: 0.3-3.0 mU/L.

In pregnant patients with treated hypothyroidism, FT4 and TSH levels should be tested every 6 weeks and LT4 dose appropriately adjusted to maintain the target TSH levels d"2.5 mIU/L (or 3 mIU/L in the2nd and 3rd trimester) [11]. Following delivery, LT_4 should be reduced to the patient's preconception dose. Additional TSH testing should be performed at approximately 6 weeks postpartum.

Patients who are TAb+ have an increased propensity for hypothyroidism to occur later in gestation because some residual thyroid function may still remain and provide a buffer during the first trimester. It is reasonable to evaluate euthyroid TAb+ women for TSH elevation approximately every 4–6 weeks during pregnancy.

Women with SCH in pregnancy who are not initially treated should be monitored for progression to OH with a serum TSH and FT_4 approximately every 4 weeks until 16–20 weeks gestation and at least once between 26 and 32 weeks gestation. Women with SCH and TPO Ab+ should be treated with LT_4.

Hyperthyroidism in Pregnancy

Hyperthyroidism is less common than hypothyroidism due to increased pregnancy losses and low fertility rate associated with this disorder[12]. Graves' disease is the most common cause of autoimmune hyperthyroidism in pregnancy, occurring in 0.1%–1% (0.4% clinical and 0.6% subclinical) of all pregnancies [13]. It may be diagnosed for the first time in pregnancy or pre-existing Graves'disease may flare up in the 1st trimester only to remit in 2nd and 3rd trimester. Less commonly thyrotoxicosis may be due to toxic multinodular goiter , toxic adenoma, subacute painful or silent thyroiditis or struma ovarii.

Another common condition is gestational thyrotoxicosis (GTT) defined as "transient hyperthyroidism, limited to the first half of pregnancy characterized by elevated FT_4, suppressed or undetectable serum TSH and negative TRAb"[14]. It occurs in about 1–3% of pregnancies and is secondary to thyrotropic effect of elevated hCG levels. It may be associated with hyperemesis gravidarum, defined as severe nausea and vomiting in early pregnancy, with > 5% of weight loss, dehydration, and ketonuria. Hyperemesis gravidarum occurs in 0.5–10 per 1000 pregnancies. Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation, hydatidiform mole or choriocarcinoma [15]. Most of the cases present with marked elevations of serum hCG.

The diagnosis of clinical hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and an elevated FT_4.

Distinguishing gestational hyperthyroidism from Graves' hyperthyroidism may be challenging because of the presence of common clinical manifestations including palpitations, anxiety, hand tremor, and heat intolerance. A diagnosis of gestational hyperthyroidism is favoured if there is no prior history of thyroid disease and no clinical signs of Graves' disease (goitre, ophthalmopathy). In doubtful condition the determination of TSH receptor antibody (TRAb) is indicated. Diagnosis of Grave's disease is supported by evidence of diffuse goiter and autoimmunity, like presence of anti-TSH receptor antibodies. In the presence of a nodular goitre, a serum total T_3 (TT_3) determination is helpful in assessing the possibility of the "T_3 toxicosis" syndrome. Total T_3 determination may also be of benefit in diagnosing T_3 thyrotoxicosis caused by Graves' disease.

Adverse outcomes associated with Hyperthyroidism in pregnancy

Poor control of thyrotoxicosis is associated with miscarriages, pregnancy-induced hypertension, prematurity, low birth weight, IUGR, stillbirth, thyroid storm, and maternal congestive heart failure. Thyrotoxic women should be rendered euthyroid before attempting pregnancy. Pre pregnancy counselling for all patients with hyperthyroidism or a history of hyperthyroidism is imperative, and use of contraception until the disease is controlled is strongly recommended. Prior to conception, a hyperthyroid patient may be offered ablative therapy (^{131}I or surgery) or medical therapy.

Surgery is a reasonable option in the presence of high TRAb titres if the mother is planning pregnancy in the following 2 years. If the patient opts for ablative therapy, she should be informed that, TRAb titres tend to increase following ^{131}I therapy and remain elevated for many months [16]. A pregnancy test should be performed 48 hours

before ^{131}I ablation to avoid radiation exposure to the fetus. Conception should be delayed for 6 months post-ablation to allow time for the dose of LT_4 to be adjusted to obtain target values for pregnancy (serum TSH between 0.3 and 2.5 mIU/L).

Management

Anti thyroid drugs

ATDs are the mainstay of treatment for hyperthyroidism during pregnancy[17]. They reduce iodine organification and coupling of monoiodotyrosine and diiodotyrosine, thereby inhibiting thyroid hormone synthesis. If the patient chooses ATD therapy, risks associated with both propylthiouracil (PTU) and methimazole (MMI) should be discussed. PTU is the preferred drug in the 1st trimester, and it is imperative to switch over to MMI from 2nd trimester. In general, initial doses of ATDs are as follows: MMI, 5–15 mg daily; Carbimazole, 10–15 mg daily; and PTU, 50–300 mg daily in divided doses.

Side effects occur in 3–5% of patients taking thionamide drugs, mostly allergic reactions such as skin rash. MMI is teratogenic and may produce several congenital malformations, mainly aplasia cutis and the syndrome of "MMI embryopathy" that includes choanal or esophageal atresia and dysmorphic facies. Patients on PTU have risk of hepatotoxicity which may occur at any time during treatment; so FDA has recommended limiting the use of PTU to the first trimester of pregnancy[18]. In exceptional conditions like MMI allergy and thyroid storm PTU can be used. Monitoring of hepatic enzymes during PTU therapy should be done.

Beta blockers are usually avoided during pregnancy. However, they can be used for a short period of time for controlling thyrotoxicosis symptoms. Long term use of beta-blockers is associated with adverse effects e.g. IUGR, fetal bradycardia and neonatal hypoglycemia, hence they should be discontinued within the first few weeks of treatment or as the symptoms resolved [19].

In women being treated with ATDs in pregnancy, FT_4 and TSH should be monitored approximately every 2–6 weeks . Aim should be to maintain the fT_4 levels in the upper non-pregnant reference range. Over treatment should be avoided to prevent development of fetal goiter and fetal hypothyroidism.

Surgery

Thyroidectomy in pregnancy is rarely indicated. If required, the optimal time for thyroidectomy is in the 2nd trimester.

Fetal surveillance

A maternal serum TRAb level should be obtained at 20–24 weeks of gestation with past or present history of Graves' disease. Fetal surveillance with serial ultrasounds should be performed in women who have uncontrolled hyperthyroidism and/or women with high TRAb levels (>3 times the upper limit of normal)[20].

Management of Gestational Hyperthyroidism

The appropriate management of women with gestational hyperthyroidism and hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended for the management of gestational hyperthyroidism.) treatment should be started if there is a persistence of hyperthyroid symptoms & abnormal TFT after 18th-20th wks as this might indicate Graves' disease.

Conclusion

Pregnancy has profound effect on the thyroid, resulting in hypothyroidism in women with limited thyroidal reserve or iodine deficiency, and postpartum thyroiditis in women with underlying Hashimoto's disease who were euthyroid prior to conception. Hypothyroidism and hyperthyroidism should be diagnosed early with screening in high risk

groups and to be managed properly to avoid foetal and maternal complications.

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Case Report

PHEOCHROMOCYTOMA MASQUERADING AS DIABETES INSIPIDUS

*Binoy Kumar Mohanty***, Arun Kumar Choudhury**, Deepak Kumar Dash*, Swayam Sidha Mangaraj*, Pratap Kumar Mishra*, Debarchan Jena*, Subash Ranjan Behera*, Anoj Kumar Baliarsinha*****

BACKGROUND

Pheochromocytomas are catecholamine secreting tumors that arise from chromaffin cells of the adrenal medulla. These are rare tumors with an annual incidence of 2 to 8 cases per 1 million people[1].The mean age at diagnosis is about 40 years, although it can occur from early childhood until late in life. They occur with equal frequency in men and women. The clinical presentation is so variable that pheochromocytoma has been termed "the great masquerade". Episodes of palpitation, headache and sweating constitute the classic triad of pheochromocytoma and are present in up to 50-70% of patients[2].The presence of all three symptoms with hypertension makes pheochromocytoma a likely diagnosis. Hypertension is classically episodic but can be sustained. Other relatively common symptoms and signs are anxiety, fatigability, nausea, constipation, angina, orthostatic hypotension and blurred vision. Polyuria is a rare presentation of pheochromocytoma and it has been described predominantly in pediatric literature [3].Here we present an interesting case who presented for evaluation of polyuria and polydipsia, but subsequently was found to have pheochromocytoma.

CASE REPORT

A 20 year old female was admitted to our department for evaluation of polyuria and polydipsia for the preceding 3 months. She was referred to us for evaluation of suspected diabetes insipidus.

24 hour input/output measurement revealed an output of 4.2 litres against an input of 3.6 litres. On initial physical examination her body weight was 45 Kg, height was 160 cm with a BMI of 17.58 kg/m2. The blood pressure was 170/90 mmHg, and the pulse rate was 90 beats/min. Rest systemic examinations were normal. The initial baseline investigations were as follows: Fasting plasma glucose-86mg/dl , 2hr 75 gm post glucose plasma glucose-132mg/dl, serum sodium-142mEq/L and potassium-3.9 mEq/ L. Renal function, thyroid function ,serum calcium, , urine R/M were normal. On enquiry she had history of occasional episodes of headache and palpitation for the preceding 1 year. The presence of hypertension in a young girl prompted us to look for secondary causes of hypertension. After excluding other causes; a work up for pheochromocytoma was done. It revealed raised urinary metanephrine- 3324 µg/24hour (N<350) and normetanephrine-5910 µg/24hr (N<600). Serum 8 AM cortisol, DHEAS and Aldosterone-Plasma renin activity were normal. Anatomic localisation was done with CECT (with adrenal protocol) which revealed an intensely enhancing heterogeneous lesion of size 6.4cm x 4.5cm x 6.5 cm in right adrenal with central necrosis(pre contrast

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HU: 20-30 and post contrast HU: 70-90)**(Figure-1)**.The patient did not have any features of familial or syndromic pheochromocytoma. She was started with alpha blocker (prazosin) for control of blood pressure. After giving titrated doses urine output dramatically decreased and after 7days it completely normalized. Dose of prazosin was gradually increased to achieve the target blood pressure (130/80 mm Hg).Patient was advised to take diet high in sodium (>5gm/day) with sufficient intake of water. After achieving adequate alpha blockade propranolol was started 2-3 days prior to surgery. Then patient was posted for open adrenalectomy. Intraoperative period was uneventful except rise in blood pressure which was managed with IV nitroprusside. Histopathology report showed polygonal cells with pleomorphic nuclei and abundant eosinophilic cytoplasm arranged in nests and trabeculae. Mitotic figures were scanty (1/10 HPF) suggestive of benign nature. Genetic study could not be done due to non-availability in our institute. After surgery blood pressure became normal. After 2 weeks of surgery, urinary metanephrine and normetanephrine were done and they were within normal limits confirming complete removal of tumor.

DISCUSSION

Adrenaline and noradrenaline are the main catecholamines produced by pheochromocytoma. Noradrenaline has α excitatory effects but adrenaline has both α and β excitatory effects. Noradrenaline can cross the blood–brain barrier slowly and inhibit anti diuretic hormone (ADH) release [4], which was the probable cause for polyuria and polydipsia in this case. ADH release is mediated by both osmolar and nonosmolar stimuli. Experiments have revealed that noradrenaline-induced inhibition of ADH release worked through a baroreceptor-mediated mechanism [5]. This baroreceptor-mediated inhibition of ADH release can be blocked with an α adrenergic antagonist, indicating that inhibition of ADH by noradrenaline acts through α adrenergic receptors [6]. Elevated blood pressure also inhibits ADH through peripheral baroreceptors by increased sympathetic stimulation [7]. Various experiments have revealed that denervation of baroreceptors abolished the diuretic effect of IV noradrenaline.

Moreover, in experimental and clinical studies, administration of noradrenaline has been seen to cause a reduction in insulin secretion [8], as well as sensitivity [9]. The combined effect is therefore hyperglycemia, which can lead to solute mediated diuresis. In our case however, she was normoglycemic and therefore unlikely to be contributing to polyuria.

Our case exemplifies that polyuria could be the predominant presenting feature of pheochromocytoma. It could be falsely attributed to diabetes insipidus if clinical suspicion is not so high. Moreover not every case of pheochromocytoma is associated with hypertension. Hypertension is episodic in 50% cases and sustained in 50 % cases. Therefore mere absence of hypertension at one point does not exclude pheochromocytoma.

There are few case reports in the literature reporting polyuria as a presenting symptom in pheochromocytoma. Such presentation is usually described in children; however rare cases in adults have also been described [10]. Our case presented with polyuria and polydipsia as the predominant complaint in an adult, leading to delay in diagnosis despite consulting several physicians. It is not known why such discrepancy exists in presentation among adults and pediatric population.

CONCLUSION

A diabetes insipidus like picture may be the presenting feature of pheochromocytoma. A prompt response to alpha blocker makes the suspicion still stronger. Early diagnosis in such cases can be life saving.

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Case Report

CHRONIC TOPHACEOUS GOUT IN A CASE OF SICKLE CELL ANEMIA

Suprabhat Giri, Namita Mohanty**, Rini George*, Suvendu Sekhar Acharya****

ABSTRACT

Sickle cell anemia is an autosomal recessive hemoglobinopathy associated with chronic hemolytic anemia and rheumatic manifestations..Despite the high incidence of hyperuricaemiadue to increased RBC turnover and impaired renal function the occurrence of gout with sickle cell disease is rare and the occurrence of tophi is still rarer.[1,2]We report a case of a sickle cell disease with chronic tophaceous gouty arthritis in a 29 year old lady whose diagnosis and treatment was delayed for 6 months before she came under our supervision.

Key Words: sickle cell anemia, gout, tophi

INTRODUCTION

Secondary gout is a well recognised complication of disorders characterised by increased nucleic acid catabolism and disordered renal function. Its notable rarity in patients with haemoglobinopathies, such as sickle cell anaemia, stimulates speculation on certain aspects of the pathogenesis of gout. The frequency of hyperuricaemia and impaired renal function in sickle cell disease is not accompanied by the expected incidence of gouty arthritis. Analysis of reported cases suggests the existence of 2 forms of arthritis associated with sickle cell anaemia- noninflammatory and inflammatory. Paradoxically, gout in these cases appears to be associated with the former, in which the pathophysiological changes probably prevent or diminish the acute inflammatory response.[3]

CASE REPORT

A 29 year old female, a known case of sickle cell disease since last 12 years presented with pain in both kneejoints and elbow jointsand multiple painful nodular swellings of increasing size on both legs (figure 1) since 6 months, generalised weakness and shortness of breath since last 1 months with past history of biliary colic. On examination patient was poorly nourished, markedly pale with mild icterus. At admission her hemoglobin was 2g/dl, sickling test positive with Hb electrophoresis revealing SS band, Sr. urea-145mg/dl, sr. creatinine-3.0mg/dl, sr. bilirubin(total)-2.5mg/dl, sr. bilirubin(direct)-0.3mg/dl, sr. uric acid-19.8md/dl and 24 hour urinary uric acid- 900mg/day suggesting an overproduction. X ray of the right foot showed sharp punched out defect with overhangin margin in 1st metatarsal and proximal phalanx with tophi seen as a soft tissue mass of intermediate density(figure 2).FNAC from a firm swelling in the right great toe showed chalky material and on polarizing microscopy revealed numerous clusters of negatively birefringent needle shaped crystals(figure 3). USG of abdomen showed multiple calculi of size 3-4mm in the lumen of gall bladder with bilateral normal sized kidney with increased echotexture. The patient was managed with packed cell transfusion, folate supplements, tramadol, hydroxyurea and febuxostat.

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Citation - *Giri S, Mohanty N, George R, Acharya S. S..*; Chronic Tophaceous Gout in A Case of Sickle Cell Anemia, Orissa Phys. J., 13 (1);2016:29-31

DISCUSSION

Studies of patients with SCA have shown a high prevalence of hyperuricemia, beginning during childhood. The initial event in the development of hyperuricemia presumably is increased synthesis of nucleic acids occurring as part of the erythropoietic response to hemolysis. Catabolism of the nucleic acids generates urate. Increased production of UA normally is compensated for by increased urinary excretion of UA. This response occurs in patients with SCA, but during the third decade of lifehyperuricosuria can be reduced probably by damage to the renal tubules caused by infarction and hypoxia resulting from sickling. Chronic NSAID use in these patients may also contribute to the nephropathy. Impairment of the compensatory renal response leads to more severe and sustained hyperuricemia, and gouty arthritis may then develop.[4]In contrast to hyperuricaemia gout is an uncommon complication of SCA.[1] It is hypothesised that this infrequent association is due to circulatory impairment resulting from congestion and thrombosis of small vessels in the synovia.[1] This prevents white blood cells from responding to chemotactic stimulus of the uric acid crystals.[1] For gout to present acutely, the presence of polymorph nuclear cells is mandatory which may be impaired due to the vasculopathy and impaired generation of chemotactic factors.[1]Also the activity of these cells is greatly reduced by the anaerobic conditions that are present in SCA.[1] Another theory put forth is that aging and degenerative changes in joints play a role for urate crystallisation in joint fluids, only moderately supersaturated with urate. However patients suffering from SCA do not enjoy a lifespan long enough for this to occur.[1]The rarity of this association may also result from a failure to recognise clinical gout, the symptoms of which may be blunted by chronic analgesic use or may closely resemble those of the acute sickle crisis.[5]So, all patients of SCA with polyarthritis should undergo serum uric acid level estimation, so that hyperuricemia can be diagnosed early and treated with uricostatic agents to prevent the development of gouty arthritis.

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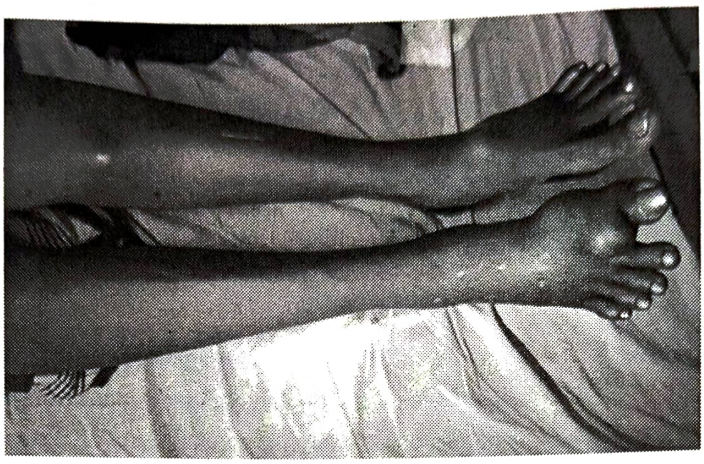
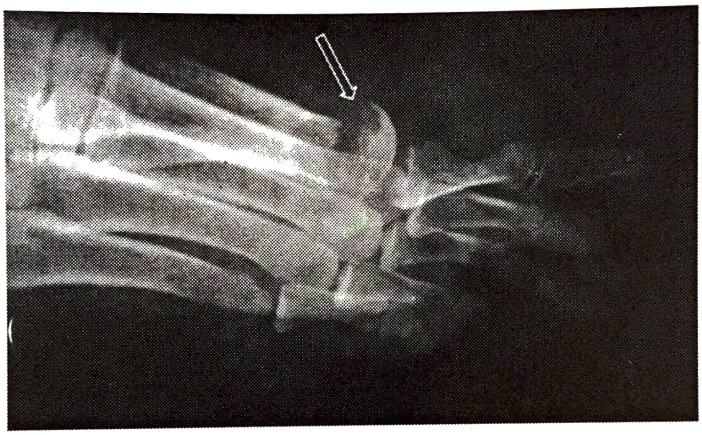


Multiple tophi over both legs



Punched out defect with overhanging margin

Needle shaped negatively birefringent crystals

Case Report

MELIOIDOSIS: A CASE REPORT

*N. K. Sundaray, **Amit Kumar, **.K.K.Jena, *** Chandan Das, ***.Pramod kumar Tudu, ***.Srikant Dhar, ****. N.K. Debta

ABSTRACT

Burkholderia pseudomallei infection is commonly seen in Southeast Asia and North Australia. It is now increasingly being reported from different parts of India. Here we present a 24 years old male who presented with fever, cough, expectoration , breathlessness , loss of appetite, loss of weight , vomiting and sleeplessness over a period of 3 months. Burkholderia pseudomallei was isolated from sputum. He was put on carbepenem and levofloxacin based on culture report. He has responded to therapy and at present, on maintenance therapy and recovering.

Key Words. *Burkholderia pseudomallei,* Melioidosis, Carbepenem, Levofloxacin

INTRODUCTION : *Burkholderia pseudomallei* (previously known as Bacillus pseudomallei) is a gram negative bacillus inhabiting soil, stagnant water and paddy field ,infection of which presents with varied manifestations. It was first reported from Rangoon as a "glander like disease" by Alfred Whitemore and C S Krishnaswamy[1]. The term "Melioidosis" was coined by Stanton and Fletcher in1932. Cases were mainly reported from Southeast Asia and northern parts of Australia. In India cases were reported initially from Tamil Nadu and Kerala. Subsequently cases also have been reported from other parts of India including Odisha[2]. The infection may remain asymptomatic or present with a local infection or with dissemination and shock with high fatality rate (19-35%)[3]. Here we present a case with predominant pulmonary disease which clinically and radiologically closely mimicking Pulmonary Tuberculosis. This case report is an effort to emphasize awareness of such infection in this part of the country.

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CASE REPORT- Mr S.A, 24 years old male from Khurdha district of Odisha, welder by profession, developed fever for past 3 months, which was initially low grade and continuous in nature, later on was more marked towards evening without any chills or rigors or sweating on defervescence. Fifteen days later he developed dry cough which soon became productive with mucopurulent sputum. Simultaneously he felt breathlessness on mild exertion, lost appetite and started losing weight(Lost 12 kg in three months). He also had occasional vomiting and frequent sleeplessness. There was no pain in chest, abdomen or in muscles and joints. He had no past history of TB or any medical illness. There was no history of similar illness or of TB in family . He was otherwise a smoker (one packet of bidi/day) for the past two years. On examination he was conscious, alert, height–1.6 metres, weight-45Kg, BMI-17.576. He had mild pallor, no icterus, cyanosis, lymhadenopathy, clubbing or pedal oedema, Temp-102ÚF right axilla at 1000h, Pulse -110/ minute BP -110/70mmHg Right arm supine posture, respiratory rate-30/minute, SpO2-98% at room air. Chest examination revealed no

Citation - *Sundaray N. K. , Kumar Amit, Jena K.K., Das C, Tudu P. K. , Dhar S, Debta N.K.* ; Melioidosis: A Case Report, Orissa Phys. J., 13 (1);2016:32-35

obvious abnormalities on inspection and percussion on auscultation revealed normal vesicular breath sounds, bilateral rhonchi and, coarse crepitations over right suprascapular, axillary, infraclavicular and mammary areas, no pleural rub. Other systems examination including skin were normal.

Investigations-Blood Hb-10.7 gm%, TWBC-13,280/cmm, DWBC-P-91.3% L-7.5% Platelet -1.96000/cmm, Urine, Renal Function Test, Liver Function Test were normal, ESR-29mm/1sthr, Widal test–ve, Mantoux was negative, X-Ray Chest PA view-Fibrocavitary lesions over Right upper zone and consolidation in the left middle zone, CT scan Chest showed multiple patches of consolidation with areas of break down within and multiple nodules in bilateral lung. Sputum for AFB over night sample and the next subsequent two days of total 3 Samples were found to be negative for Mycobacterium. Sputum examination revealed gram negative bacilli on smear and on culture media to be B pseudomallei sensitive to Amikacin, Piperacillin, Ciprofloxacin, Ceftriaxone, Imipenem Blood and urine culture- no growth.

Fig-1 X-Ray Chest-

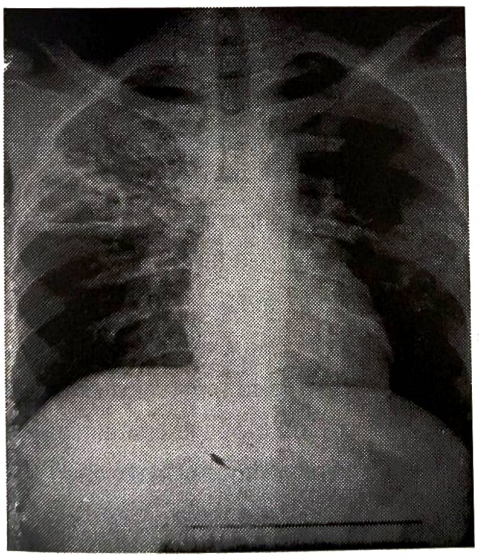
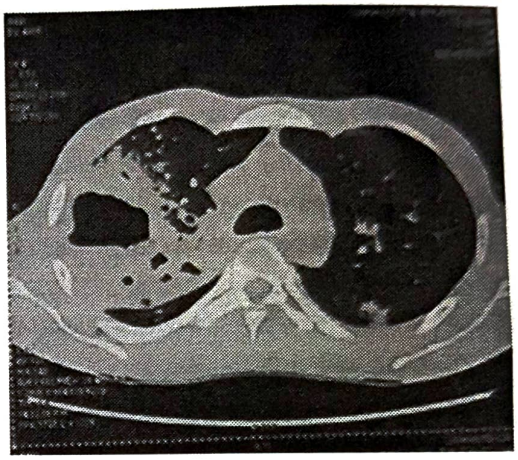
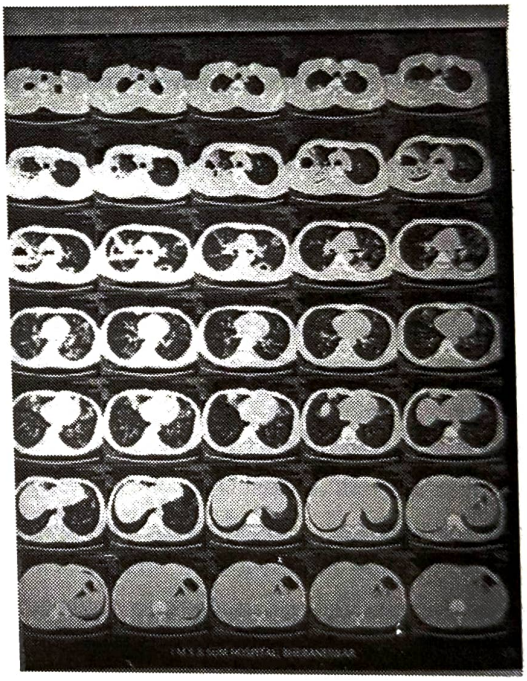


Fig-2 CT Scan Chest





He continued to be febrile despite of giving antibiotics. He was put on Inj Meropenem 1gm IV 8hrly and levofloxacin 750 mg orally once daily based on the sensitivity pattern. He continued to be febrile and lost 6kg in one week. The sputum was mucoid with greenish tinge. After 6days he started showing improvement continued to do so and was

discharged on request with advice to continue same treatment for total two weeks to be followed by maintainance Doxycycline 100 mg BD along with sulphamethoxazole trimethoprim (800mg +400mg) orally BD along with folic acid 5mg OD for 3 months and is doing well on review.

DISCUSSION: Melioidosis occurs as a result of direct inoculation, ingestion or through droplet transmission. Though healthy persons can be infected, persons who are immunocompromised due to DM (upto 76% in one report), Renal disease(3.2 in 1000 cases (2.2-4.8))[6], HIV, alcohol consumption, neoplasia, prior respiratory diseases like bronchiectasis, COPD, trauma, pregnancy[3] are more prone[4,5]. Usually patients are males from rural back ground with age of susceptibility varying between 4 years to 60 years of age. Clinically it may be asymptomatic, localised infection in form of abscesses in skin, lymph node, bone, visceras or it may present with infection giving rise to sepsis and septic shock. The incubation period varies from 1 to 21 days but may extend to months to years since the organism can remain dormant inside the macrophages. Duration of presenting symptom varied in one study from seven days to six months with predominant manifestation being fever. Our patient is a 24 years old male from a village and contact through all routes are possible though inhalational exposure is most likely due to predominant respiratory presentation. He did not have any risk factors enumerated above but he was a smoker. His main symptom was, continous fever of three months duration. Our case typically manifested with increased pulmonary involvement. Diagnosis is suspected on the clinical picture of fever cough, weight loss, lymphadenopathy, abscesses, sepsis and PUO. Cases are missed due to protean manifestation of the infection mimicking diseases like TB[5] unawareness, nonavailbilty of experienced microbiologist. In suspected cases smear examination for bipolar gram negative rods followed by culture of appropriate fluid/ secretion/excretion and demonstration of four fold rise in serum antibody to the organism remains confirmatory. Culture remains the gold standard test while indirect haemagglutination test is of limited value and PCR amplification technique for detecting DNA of the bacilli is useful. Our patient was confirmed based on sputum culture. In some cases X-Ray chest may reveal small infiltrate, discrete, diffuse or patchy lobar or multi lobar consolidation, necrotising lesions, cavitation, abscesses with fluid level and pleural effusion. Our case had fibro-cavitary lesions involving right upper lobe. The drug of choice is Ceftazidine a newer generation cephalosporins[2,3]. Our case was resistant to it which has been seen in other cases also[7]. Carbepenem is effective as an alternate to ceftazidine[3] which was exhibited in this case. Duration of treatment is recommended for two weeks of intensive therapy followed by three months of maintainace therapy which was also recommended in this case. Treatment failure and relapse are known[4]. Fatality do occur despite drugs which could be due to severe infection or late diagnosis[3].

CONCLUSION. This case in question had long standing history of fever, sputum production and bilateral cavitatory disease that mimics clinical and radiological features of pulmonary tuberculosis, however sputum demonstration of AFB was lacking which made us inquisitive in examination for other possible causes. This patient was diagnosed at the first instance due to correct microbiological support which highlights the importance of high index of suspicion in those atypical cases. The disease is amounting to endemic proportion and should be kept in mind while dealing with sepsis syndrome. Early diagnosis and intensive therapy followed by maintenance phase is rewarding. The presentation aims at creating awareness about the prevalence of Melioidosis in this part of the country.

Source of support – Nil

Conflict of Interest – None declared

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Case Report

A RARE CASE OF DERMATOMYOSITIS WITH AUTOIMMUNE HYPERTHROIDISM

Nishant Debta, D Ramchandran*, Subash Behera**, Sarita Behera***, Sarat Ch Singh***, S K Tripathy*****

ABSTRACT

Dermatomyositis is an inflammatory myopathy characterized by progressive and symmetrical muscle weakness with a characteristic rash which may accompany or precede myopathy. Its association with thyrotoxicosis is very rare i.e<1% in both the condition myopathy is present but emg ,creatine kinase are normal in thyrotoxicosis ,moreover histological and skin manifestaions will differentiate each other. We report a case of dermatomyositis with autoimmune hyperthyroidism.

INTRODUCTION

Dermatomyositis affects both children and adults and women more than men. The estimated prevalence is approximately 1 in 50,000.It was 1st detected by Prof. Hans Unvericht in 1887. It is characterized by rash and proximal muscle weakness, like heliotrope rash, gottronpapule , V sign, shawl sign , mechanic hands and sometimes without myopathy.It is usually associated with malignancy and connective tissue disorder. It is rarely associated with graves disease i.e<1 %(2). We report a case of dermatomyositis with thyrotoxicosis.

CASE REPORT

A 34 yr male presented with continued fever for 15 days with weakness of both lower limbs for 15 days associated with myalgia not associated with altered sensorium, vomiting ,convulsion,or bladder bowel involvement.

On examination patient was conscious oriented febrile temp100F, PR-120/min, BP -130/70 , there was b/l proptosis and erythematous rash over knuckles of hand , with fine tremor and without thyromegalyand rest of general examination revealed no abnormality.Oncns examination power on upper limb was 3/5 and lower limb 0/5 predominantly proximal myopathy with normal deep tendon reflex and b/l plantar flexor and rest of cns examination was normal.

Investigations: patient Hb was 12.7, ESR-100, TLC-9600 and CRP(Q)-131. Renal function test and liver function test were normal. CPK was 680IU and LDH was 773. Thyroid function test reveals hyperthyroidism with FT3-5.14,FT4-24.8,TSH-0.038.

ENA profile was negative and Anti TPO was positive. EMG reveals myopathic pattern

USG of neck and abdomen& pelvis were normal.Thyroid scan reveals no abnormality. Muscle biopsy was suggestive of dermatomyositis as muscle fibres were separated by increase in endomysial connective tissue and atrophy of muscle fibre.

Patient was diagnosed a case of DERMATOMYOSITIS WITH THROTOXICOSIS and was started with prednisolone 1mg /kg body weight andneomercazole 10mg tds.

*Postgraduate,**Senior Resident,***Asst Prof,****Asso Professor SCB Medical College, Cuttack

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DISCUSSION

Dermatomyositis is one of the idiopathic inflammatory myopathy. In 1975 Bohan and Peter set a criteria ,of the 5 criteria 4 are 1)progressive proximal symmetrical weakness, 2)elevated muscle enzymes 3)abnormal emg abnormal muscle biopsy and 5th was presence of mpatible cutaneous disease. The characteristic and nogonomic cutaneous features are heliotrope rash and ron papules. The heliotrope rash consist of a violaceous dusky erythematous rash with or without edema in a symmetrical distribution involving periorbital skin. Gottron 's papules are found over bony prominences particularly MCP,PIP, DIP joints. The lesion consist of violaceous papules and plaques. Other skin changes are V sign, SHAWL sign, HOLSTER sign. Myopathy affects the proximal muscle and is progressive and symmetrical associated with myalgia. Dysphagia signifies a rapidly progressive course and associated with poor prognosis. Arthritis is present in 25% of cases. Pulmonary disease occurs in 15-65% of cases, most ccommonly interstitial pneumonitis. The reported frequency of malignancy with DM is varied from 6 to 60%. Drugs associated DM are due to hydroxyurea, NSAIDS, quinidine ,isoniazid.

The diagnosis of DM is suspected in clinically compatible cutaneous findings. Creatinine kinase and LDH are most useful test for following response to therapy. Anti Jo1 antibody is predictive for pulmonary involvement and antiMi 2 occurs in 25-30% of patients almost specific for DM. Those with antiSRP antibody has worst prognosis than with antiMi2. Children with DM it was suggested that elevated Von willebrand factor associated with active disease. An evaluation of malignancy should be considered in all patients with DM.(1)

DM is rarely associated with thyrotoxicosis i.e less than 1%, it is usually associated with throidmalignancy.

Histologic features of DM is a group of atrophic fibres particularly prominent at the periphery of fesicles ,it is said that perifascicular atrophy is sufficient for diagnosis if inflammation is absent whereas thyrotoxic myopathy has myofiber necrosis ,regeneration and interstitial lymphocytosis.(3)

Oral prednisolone is the treatment of choice with 1mg /kg body weight and tapered slowly with evidence of efficacy. Other drugs are azathioprine, methotrexate, mycofenolatemofetil, rituximab, cyclophosphamide and tacrolimus. For regractory DM IVIg can b tried.

CONCLUSION

Dermatomyositis is an idiopathic inflammatory myopathy associated with malignancy and connective tissuedisorder. Our case report is about its coexistent with thyrotoxicosis probably by autoimmune mechanism.

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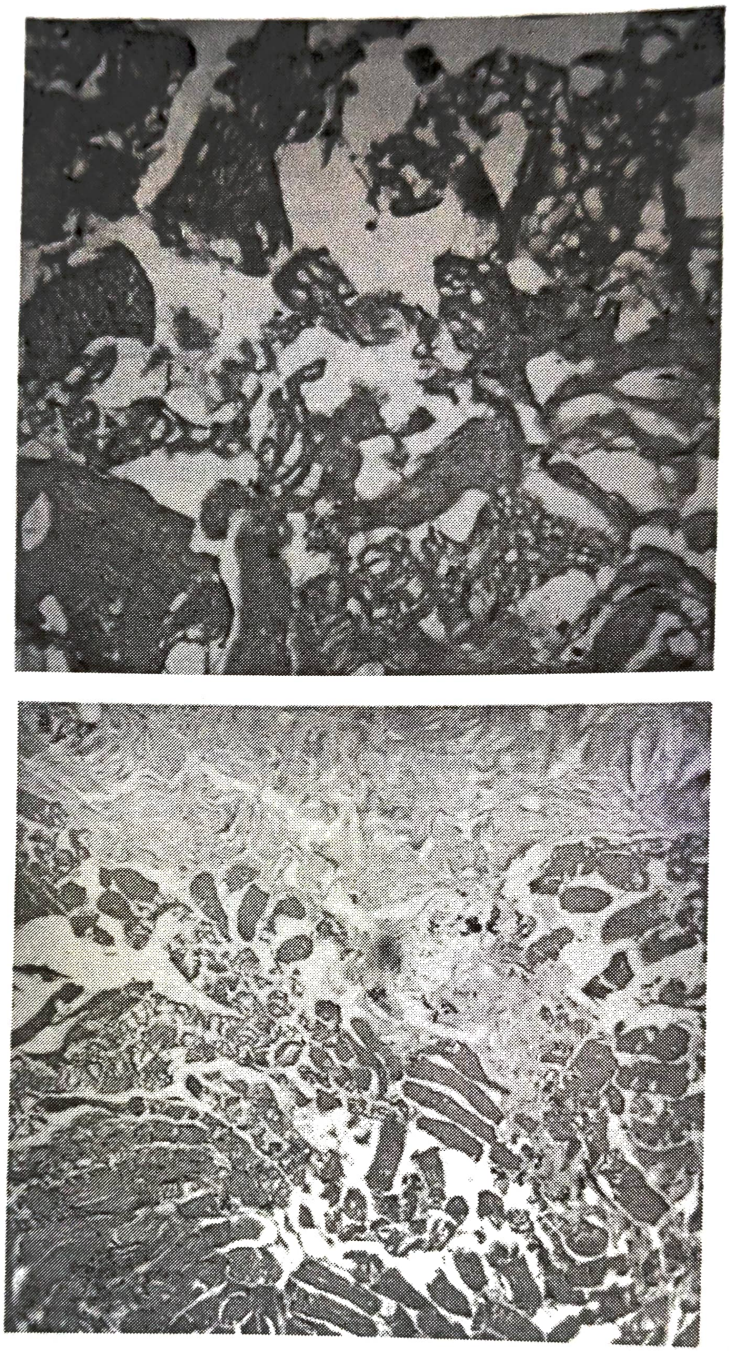

Cross section of muscle biopsy demonstrating muscle fiber atrophy.

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