

Assam Journal of Internal Medicine

Official Journal of Association of Physicians of India, Assam Chapter

A PEER REVIEWED JOURNAL

BIANNUAL PUBLICATION – January 2018 (Next issue- July, 2018)

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Edited, printed and published by :

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ASSAM JOURNAL OF INTERNAL MEDICINE

Official Journal of Association of Physicians of India, Assam Chapter

Editor in Chief : PROF. SANJEEB KAKATI

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Dengue : An Emerging Threat

B N Mahanta*

Dengue is an important arboviral illness in humans transmitted by mosquitoes of the genus *Aedes*, which are widely distributed in subtropical and tropical areas of the world. *Aedes albopictus* is more cold tolerant than *Aedes aegypti*, so it can survive and transmit virus in the more temperate regions. There is rising incidence of dengue in recent decades with geographical expansion and estimated 40%-50% of the world's population are at risk for the disease in tropical, subtropical, and, recently, more temperate areas. Viraemia appears before the onset of symptoms and lasts an average of five days after the onset. Strong suspicion of Dengue should be made in individuals who present with high fever (104°F/40°C), retro-orbital headache, muscle and joint pain, nausea, lymphadenopathy, vomiting, and rash and who have travelled within 2 weeks of symptom onset to an area where principal vectors are present and dengue transmission is ongoing. Evidence of plasma leakage with any of the features like rise of average HCT for age & sex by >20%, more than 20% drop in hematocrit following volume replacement compared to baseline. Signs of plasma leakage are pleural effusion, ascites & hypoproteinemia etc.

Laboratory criteria for the diagnosis of dengue include one or more of the following, which are used to detect the virus, viral nucleic acid, antibodies or antigens, or a combination thereof: demonstration of a fourfold or greater change in reciprocal immunoglobulin G (IgG) or IgM antibody titres to one or more dengue virus antigens in paired serum samples; demonstration of dengue virus

antigen in autopsy tissue via immunohistochemistry or immunofluorescence or in serum samples via enzyme immunoassay (MAC-ELISA, IgG ELISA, nonstructural protein 1 [NS1] ELISA, EIA); detection of viral genomic sequences in autopsy tissue, serum, or cerebral spinal fluid (CSF) samples via reverse-transcriptase polymerase chain reaction (RT-PCR) assay: RT-PCR provides earlier and more specific diagnosis and less frequently, isolation of the dengue virus from serum, plasma, leukocytes, or autopsy samples.

During the early phase of the disease (first 4-5 days), virus can be detected in serum, plasma, circulating blood cells, and tissues. Virus isolation, nucleic acid detection, and antigen detection are more useful to diagnose infection. At the end of the acute phase of illness, serology becomes the method of choice. Dengue fever is typically a self-limiting disease with a mortality rate of less than 1% when detected early and with access to proper medical care. Severe dengue (*dengue hemorrhagic fever and dengue shock syndrome*) can occur in a small percentage of persons who have previously been infected by one dengue serotype and subsequently infected by a second serotype (Secondary infection). The severe cases develop complications due to bleeding and endothelial leak, mostly between 3rd to 7th day of illness. When treated, severe dengue has a mortality rate of 2%-5%, but, the mortality rate may be as high as 20% if left untreated.

Mainstay of treatment of dengue is with correction of intravascular volume deficits and should be corrected with isotonic fluids such as Ringer lactate solution. Boluses of 10-20 mL/kg should be given over 20 minutes and may be repeated. If this fails to correct the deficit, the

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hematocrit value should be determined. If it is rising, limited clinical information suggests that a plasma expander may be administered. Starch, dextran 40, or albumin 5% at a dose of 10-20 mL/kg may be used. Wills BA et al in their publication entitled "Comparison of three fluid solutions for resuscitation in dengue shock syndrome" published in N Engl J Med has suggested that starch may be preferable because of hypersensitivity reactions to dextran. If the patient does not improve after infusion of a plasma expander, blood loss should be considered. Patients with internal or gastrointestinal bleeding may require transfusion, and patients with coagulopathy may require fresh frozen plasma. After patients with dehydration are stabilized, they usually require intravenous fluids for no more than 24-48 hours. Intravenous fluids should be stopped when the hematocrit falls below 40% and adequate intravascular volume is present. At this time, patients reabsorb extravasated fluid and are at risk for volume overload if intravenous fluids are continued. One should not interpret a falling hematocrit value in a clinically improving patient as a sign of internal bleeding. Platelet and fresh frozen plasma transfusions may be required to control severe bleeding. Platelet count between 40000 cells/ μ L of blood and above 10000 cells/ μ L of blood with evidence of bleeding and any patient with platelet count below 10000/mm³ of blood are indications for platelet transfusions. A case report demonstrated good improvement following intravenous anti-D globulin administration in 2 patients. The authors proposed that, as in immune thrombocytopenic purpura from disorders other than dengue, intravenous anti-D produces Fc γ receptor blockade to raise platelet counts.²

Dengue in pregnancy must be carefully differentiated from pre-eclampsia. An overlap of signs and symptoms, including thrombocytopenia, capillary leak, impaired liver function, ascites, and decreased urine output may make this clinically challenging. Pregnant women with dengue fever respond well to the usual therapy of fluids, rest, and antipyretics. An awareness of the clinical and laboratory manifestations of dengue in pregnancy should allow its early recognition and the institution of appropriate treatment.

Adequate care of co-morbid conditions in cases of dengue are to be provided to minimise mortality. Patients who are resuscitated from shock rapidly recover. Patients

with dengue hemorrhagic fever or dengue shock syndrome may be discharged from the hospital when they meet the following criteria: Afebrile for 24 hours without antipyretics, good appetite, clinically improved condition, adequate urine output, stable hematocrit level, at least 48 hours since recovery from shock, no respiratory distress and platelet count greater than 50,000 cells/ μ L.

The only way to truly prevent dengue virus acquisition is to avoid being bitten by a vector mosquito and control of vector mosquito. One vaccine is currently approved for the prevention of dengue infection. Sanofi Pasteur registered Dengvaxia (CYD-TDV), a live recombinant tetravalent vaccine, in several countries in late 2015-2016, with Mexico being the initial country to register the vaccine in December 2015. The vaccine is given in 3 doses at age 0, 6, and 12 months. It underwent testing in more than 30,000 volunteers and was shown to reduce the risk of severe illness and hospitalization by as much as 30% in individuals previously infected with one or more strains. The vaccine proved less effective in persons who were not previously exposed to dengue and in areas with a lower burden of disease.^{3,4} Owing to concern that the vaccine may act like an initial dengue infection in this second group of individuals not previously infected with the virus, with additional exposure to a second serotype placing these individuals at increased risk of severe dengue, the WHO released a position paper in July 2016, stating that countries should consider introduction of vaccine as a part of an comprehensive dengue control strategy only where epidemiologic data indicate a high burden of disease.^{5,6} Seroconversion alone does not predict protection. Several other immunogenic tetravalent vaccine candidates have been developed and are undergoing clinical trials.

Strengthening of routine surveillance system for detection of early warning signs (EWS) of an outbreak with use of digital technology has potential to avert an epidemic. Both epidemiological and vector surveillance in routine system is essential along with strengthening primary care facilities and referral linkage. Community participation in different preventive activities for example anti-mosquito drives, cleanliness drive, linking National Vector Borne Disease Control Programme (NVBDCP) with "Swachh Bharat Abhiyan" and awareness building for getting early access to health care facility may further reduce the morbidity and mortality. Uniform protocol of treatment in

different levels of clinical service delivery may be achieved by capacity building and provision of adequate infrastructure with quality control.

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A Study of Risk Factors, Clinical and Laboratory Profile of Severe Dengue Cases

Yashaswini L S*

Abstract

Background: Dengue is a major health problem in India. The understanding of the factors which predispose to the infection and which are involved in its progression is fundamental for improved clinical outcomes. This study was initiated with the aim of identifying the patient population at risk and comorbidities involved in the development of complications. **Methods:** This was an observational study in which 432 cases were evaluated with respect to data regarding demographics, complications and co morbid metabolic diseases. **Results:** There was predominance of males in the age group 21-30 years. Fever was the major presenting complaint. Other prominent symptoms were headache (58%), chills (73%), vomiting (41%), myalgia (71%), joint pain (65%), and bleeding manifestations (44%). Common co morbid conditions present in the cases assessed were Diabetes mellitus (7.1%), hypertension (5.8%), alcoholism (22.7%), and smoking (23.6%). 88% cases in the study had thrombocytopenia at admission. Common altered lab parameters observed in the study were raised hematocrit (43.3%), leucopenia (51.9%), raised SGOT/SGPT (36.6%). GB wall edema was the most common USG finding observed in 70.1% cases, followed by ascites (48.4%), pleural effusion (40.7%). Complications like bradycardia were seen in 12.0% cases, also congestive cardiac failure in 4.6% cases, followed by shock in 15% cases. These complications were commonly noted in those cases with co morbid conditions which prolonged their stay in the hospital. **Conclusions:** Comorbidities like diabetes mellitus, hypertension, and alcoholism predispose to dengue infection and are liable to cause serious complications. Knowledge of this can prompt early triage, careful monitoring, clinical intervention and reduction of morbidity.

INTRODUCTION :

The word dengue is believed to have originated from Swahili language 'ki denga pepo', which describes sudden cramp like seizure¹. The first epidemic occurred in Manila, Philippines in 1953–54, followed by Bangkok in 1958, and Singapore, Malaysia, and Vietnam in the early 1960s. In India, the first major epidemic illness clinically compatible with dengue was reported from Madras in 1780, which later spread all over the country. Later, an outbreak of dengue like illness was reported in 1956 from Vellore, Tamil Nadu and since then, it has persisted in various parts of the country.² Dengue fever is caused by a Flavivirus and transmitted by bite of *Aedes Aegypti*. So, outbreaks of Dengue are commonly reported during rainy season due to water stagnation which promotes mosquito breeding.

WHO has classified Dengue as Dengue fever, Dengue hemorrhagic fever and dengue shock syndrome³. Clinically

the disease has 3 phases- febrile phase, critical phase, recovery phase. Complications of Dengue develop during critical and recovery phase. Recently, Dengue has been classified as severe and non-severe Dengue. Severe Dengue is diagnosed when patients develop any of following- Dengue shock syndrome, Pleural effusion, Ascites, ARDS, Bleeding symptoms, elevation of liver enzymes, altered consciousness, and congestive cardiac failure¹³. Patients prone to develop severe dengue are children, females, elderly (65years), obese, Diabetics, hypertensives and patients with kidney disease.¹³

This study was initiated keeping in view possibility of identifying patient population prone to develop severe Dengue.

OBJECTIVES OF STUDY :

1. To assess various comorbidities present in the cases
2. To study clinical and laboratory profile of severe dengue cases
3. To evaluate association between comorbid conditions and severity of the disease.

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METHODS :

The study was conducted on serologically confirmed cases of dengue infection in the inpatient Medicine department of Sree Rajarajeswari Medical College, Bangalore between 1st of May 2016 and 31st of July 2017.

INCLUSION CRITERIA-A total of 432 patients, presenting with fever and diagnosed as dengue based on NS1, IgM or IgG positivity were included in the study.

EXCLUSION CRITERIA-Malaria, Leptospirosis, Enteric, Respiratory and Urinary tract Infections were excluded by appropriate tests.

Clinical data were collected through interviewing the patients or their attendants for various comorbid conditions and meticulous physical examination. Reports of hematological investigations, dengue serology, liver function tests, ECG, 2D Echocardiography, renal function tests, USG Abdomen, Chest X-ray were analyzed. Patients were followed up during the course of their stay in the hospital.

RESULTS :

The involvement of all age groups, especially an adult predominance was observed. The mean age of dengue patient was 34 years and most belonged to the 21-30 year age group, which included 202 patients (46.8%)

Table 1: Age distribution of patients studied

Age in years	No. of patients	%
<20	30	6.9
21-30	202	46.8
31-40	121	28.0
41-50	58	13.4
51-60	11	2.5
>70	10	2.3
Total	432	100.0

302(70%) patients were males and 130(30%) were females.

Table 2: clinical features of dengue fever

Clinical features	No of patients	Percentage
Chills	315	73.0
Headache	250	58.0
Pain abdomen	112	26.0
Vomiting	177	41.0
Myalgia	306	71.0
Joint pain	280	65.0
Jaundice	34	8.0
Retroorbital pain	164	38.0
Seizures	9	2.0
Bleeding symptoms	190	44.0
Breathlessness	21	5.0

Fever was the most common presenting symptom in this study. Fever was present in all patients and was predominantly of intermittent type and in majority i.e. 293(68%) patients, fever was of 3-6 days duration. Mean duration of fever was 4 days and ranged from 1-15 days. Other predominant symptoms and signs are shown in ‘Table 2’

The most common comorbid condition associated was smoking (23.6%). Others are shown in table 3

Table 3: Distribution of comorbid conditions in patients

Comorbid conditions	No of patients	Percentage
Diabetes mellitus	31	7.1
Hypertension	25	5.7
Ischemic heart disease	6	1.3
Rheumatic heart disease	2	0.4
Alcoholism	98	22.6
Smoking	102	23.6
Chronic kidney disease	2	0.4

Table 4: Distribution of patients according to platelet count

Platelet count at admission	Number of patients	Percentage
<10000	26	6
11-20000	121	28
21-50000	108	25
51-100000	129	30
>1 lakh	48	11

The range of platelet count at admission was 5000 – 186000/cmm, with a mean value of 80195/cmm. Thrombocytopenia was observed in 384 patients (88%)

Table 5: Distribution of patients with altered lab parameters

Lab parameters	No of patients	Percentage
Raised hematocrit	187	43.3
Leucopenia	224	51.9
Hyperbilirubinemia	8	1.9
Raised SGOT/SGPT	160	37.0
Raised CPK	85	19.7
Uremia	4	0.9
Raised amylase	2	0.5

Majority of patients had leucopenia, hemoconcentration and raised liver enzymes. Raised serum amylase levels were the least common.

Table 6 : SGOT/SGPT distribution of patients studied

	No. of Patients (n=100)	%
SGOT (IU/L)		
< 100	116	27.0
100 - 300	190	44.0
300 - 600	108	25.0
> 600	18	4.0
SGPT (IU/L)		
< 100	103	24.

Table 7 : USG/Chest XRay findings distribution

Findings	No of patients	Percentage
GB wall oedema	303	70.1
Ascites	209	48.4
Pleural Effusion	176	40.7
Hepatomegaly	122	28.2
Splenomegaly	54	12.5

176 (40.7%) patients had evidence of pleural effusion, 209 (48.4%) had ascites, 303 (70.1%) had GB wall edema, 122 (28.2%) had hepatomegaly and 54 (12.5%) had splenomegaly. These findings were mostly seen in patients with thrombocytopenia.

Table 8 : Complications developed during course of stay in the hospital

Complications	No of patients	Percentage
ARDS	4	0.9
Bradycardia	52	12.0
Myocarditis	20	4.6
Encephalitis	2	0.5
Seizures	4	0.9
Hyponatremia	22	5.1
Shock	67	15.5

Most common complication during the course in the hospital was hypovolemic shock, followed by bradycardia. Altered sensorium was the least common complication observed.

Table 9: Distribution of complications with comorbid conditions

comorbidities	ARDS	Bradycardia	Myocarditis	encephalitis	seizures	hyponatremia	shock
DM	2	15	7	0	1	6	30
HTN	2	20	4	0	0	14	20
IHD	0	4	0	0	0	0	4
RHD	0	0	0	0	0	0	0
Alcoholism	0	0	2	0	2	3	2
Smoking	0	0	11	9	0	0	0
CKD	0	0	0	0	0	0	1

As depicted in the above table complications were mostly seen in diabetics, hypertensives and alcoholic patients.

DISCUSSION :

Bangalore is one of the big cities in India where dengue epidemics are becoming common during rainy season. In this study, majority of cases were adults with the largest proportion being in the age group of 21-30 years. This may be due to the fact that most of them are working population, construction site laborers & travelers. Habitats for *Aedes aegypti* are domestic containers, stagnant water, ornamental containers and roof gutters. These findings were comparable with a study conducted

by Mukherjee S et al⁴ in which 70% of the patients were aged 15-30 years.

In our study, 70 (70%) patients were male and 30 (30%) were females with a male to female ratio of 2:1. This is due to the fact that males predominantly form the working population & more prone to infection by mosquito bite in a day time. These findings were comparable with a study conducted by Mukherjee S et al⁴ in which male to female ratio were 3.3:1. Similar results were also observed in studies conducted by Raiker S R et al⁵ and Ahmed S et al⁶. In the present study all cases (100%) had fever. The typical 2-7 days fever as described by WHO was found in 68 cases (68%). Severe body ache, which is reported as prominent symptom in dengue, was also seen in this study (71%). Other common clinical features included chills and rigor, vomiting and nausea, headache, melena, joint pain, abdominal pain, rashes. This is very similar with several other studies done in various other parts of India.^{4,5,6}

282(65%) patients in our study were classified to be having severe Dengue, out of which 181(64%) were males and 101(36%) were females. This is in comparison to that found by Natwar Lal Sharma et.al in their study.⁹

187(43.3%) patients had raised hematocrit and 224(51.9%) had leucopenia at admission. This was comparable to findings obtained by Panji et al in their study. Raised hematocrit and leucopenia were associated with higher rates of ICU admission.¹¹

Liver enzymes were elevated in 160 (36.6%) patients in our study. 44% of patients had mild elevation of SGOT (100-300) while 43% had moderate elevation of SGPT (300-600). However in studies by Natwar Lal Sharma⁹ and Panji et al¹¹, SGOT elevation was more than SGPT.

176 (40.7%) patients developed pleural effusion in the course of the disease. 81 cases had right pleural effusion, 46 had left pleural effusion and 50 had bilateral effusion. In Natwar Lal Sharma study⁹, 12% cases had right pleural effusion, 6% had left pleural effusion and 14% had bilateral effusion. Similar results were observed in Pushpa et al⁷ and Malavige GN⁸ et al studies.

70.1% cases in our study had GB wall edema, 28.2% had hepatomegaly and 48.4% had ascites. In a study by H Kaur et al 28% cases had GB wall edema, 31% had

hepatomegaly, and 44% had pleural effusion. Significant association between GB wall edema, pleural effusion and low platelet count was demonstrated in their study.¹²

In the present study, 20 cases developed heart failure, 2 encephalitis, 2 cases had pancreatitis, and 4 patients developed uremia. In a study by H Kaur et al, 6 cases had developed heart failure, 2 encephalitis, 2 developed pancreatitis, and 3 developed uremia.¹²

In the present study, it was observed that presence of comorbidities like diabetes mellitus, Hypertension, alcoholism make the patients more susceptible to develop severe Dengue. Similar findings were observed by Pang J et al¹⁴, Mozzam F et al¹⁵ and Figueiredo et al¹⁶ in their studies. Perez et al demonstrated significant relation between comorbidities and Dengue related deaths¹⁸. However, Shahid et al failed to show statistical association between morbidities and Dengue hemorrhagic fever.¹⁷

Mean duration of hospital stay was 6 days for severe dengue cases and 4 days for non-severe cases. Findings were similar in Mishra S et al study¹⁰. Duration of hospital stay was almost similar in both groups in Natwar Lal Sharma et al study⁹. All patients improved and deaths were reported in our study.

CONCLUSION :

The importance of comorbidities in dengue cannot be overlooked. Age group of 60 years or older, diabetes, hypertension, alcoholism, and two or more pre-existing comorbidities were independent risk factors for development of severe Dengue. Though their relationship with severe and complicated disease was not statistically significant in our study it is important to note that such cases developed complications like ARDS, heart failure, renal failure, shock, pleural effusion, and encephalitis which were important contributors of morbidity. Hematocrit rise and rapid platelet count drop at presentation were significantly associated with severe dengue.

Though the sample size was small it provides preliminary evidence that dengue patient with diabetes, hypertension need extra medical care to avoid the above complications. However, larger studies are needed in this regard.

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Correlation between Epidermal Growth Factor Receptor Mutations, ALK rearrangement and clinicopathological features in Non–Small Cell Lung Cancers

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Abstract

Introduction: Lung cancer is the leading cause of death by cancer worldwide. Non-small cell lung cancer (NSCLC) constitutes about 85% of all lung cancer. A subgroup of patients with NSCLC has specific mutations in the EGFR gene and ALK gene rearrangement. Here, we investigated the relationship between EGFR mutation, ALK gene rearrangement and clinicopathologic features among these patients. **Objective:** To study the Correlation between Epidermal Growth Factor Receptor Mutations, ALK rearrangement and clinicopathological features in Non–Small Cell Lung Cancers. **Materials and Methods:** This is an institutional based prospective study. A total of 100 diagnosed Lung cancer patients were taken. Tumor specimens obtained during diagnostic procedures from patients and after pathological confirmation the paraffin-embedded material was subjected for EGFR mutation analysis and ALK detection by IHC. **Results:** During the study period, a total of 100 lung cancer patients were taken and 19(19%) patients were positive for EGFR mutations, 2(2%) patients showed ALK rearrangement (by IHC). It was observed that EGFR Mutations were found more frequently in females than in males (34.61%vs. 13.51%), in never-smokers than in smokers (42.1%vs. 4.83%) and in younger (<60yrs) age group. Chest pain (24.48%), Hemoptysis (22.22%) and cough (18.98%) were the predominant presenting symptoms in patients harbouring EGFR mutations. The frequency of EGFR mutations was higher in those with Adenocarcinoma histology (34.05%) and only single patient of squamous cell carcinoma was positive for EGFR mutation. ALK was positive in two patients of either gender both with adenocarcinoma histology. Both these patients were non smokers. **Conclusion :** From the study we conclude that EGFR mutations were significantly related to Patient gender, histology and smoke exposure. ALK rearrangement was observed in patients with adenocarcinoma histology.

KEY WORDS : Epidermal growth factor receptor (EGFR), Non-small cell lung carcinoma (NSCLC), Anaplastic lymphoma kinase (ALK), tyrosine kinase inhibitor (TKI).

INTRODUCTION :

Lung cancer is the most common cause of cancer-related death in men and women worldwide, responsible for over 1 million deaths annually.¹ Each year, more people die of lung cancer than of the next three leading causes of cancer death combined: breast, colon, and prostate cancer. Despite advances in surgical techniques and combined therapies, lung cancer remains a disease with a dismal prognosis. Although 1-year survival has improved over the past few decades, overall 5-year survival has remained relatively unchanged at 12% to 16% over the

past 30 years. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes, it is the commonest cancer and cause of cancer related mortality in men.²

Treatment decisions for patients with lung cancer were historically based on tumor histology. The understanding of newer molecular targets and driver mutations in the tumor has led to the development of targeted treatment modalities. In 2004, driver mutations in the epidermal growth factor receptor (EGFR) gene, a membrane-bound receptor tyrosine kinase (RTK) that regulates cell growth, were discovered in NSCLC, especially in adenocarcinomas.^{3,4} These mutations were strongly associated with therapeutic sensitivity to tyrosine kinase inhibitor (TKI) drugs that inhibited the tyrosine kinase (TK) function of EGFR.

The prevalence of EGFR mutations varies widely based on the ethnicity of the population with highest among East Asians (30–60%)⁵ and significantly lower in

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Caucasians (5–15%).⁶ Studies from India have reported the frequency of EGFR mutations to be between 22% and 40%, which is lesser than that reported from the East Asian populations.⁷⁻⁹

Women, Asians, those who never smoked, and adenocarcinoma patients with bronchioloalveolar subtype showed an increased response to EGFR tyrosine kinase inhibitors in a subgroup analysis.^{4,10,11} Furthermore, EGFR mutations were significantly more frequent among those who never smoked, those with adenocarcinoma histology, those of East Asian ethnicity, and women in NSCLC.¹²

The EML4-ALK fusion oncogene represents one of the newest molecular targets in NSCLC. Initially reported in 2007 by SODA et al.¹³, translocations involving the ALK (2p23) and the echinoderm microtubule-associated protein-like 4 (EML4) (2p21) genes are detected in 2–7% of lung adenocarcinomas and are responsible for a constant and additive ALK-enhanced kinase activity favouring proliferation, changes in cytoskeleton, migration and survival.^{14,16} EML4-ALK possesses potent oncogenic activity both in vitro and in vivo. This activity can be effectively blocked by small molecule inhibitors that target Anaplastic lymphoma kinase (ALK), which supports a role for EML4-ALK as a key driver of lung tumorigenesis.^{15,16}

In this study, we examined the EGFR mutational status, ALK rearrangement and correlated with clinicopathologic features in patients with NSCLCs.

MATERIALS AND METHODS :

This was a hospital based prospective study conducted in the Department of Pulmonary Medicine, Gauhati Medical College, Guwahati, Assam, from Dec 2014 to April 2016.

Patients and specimens:

A total of 100 patients were included in the study out of which, 74 were males and 26 were females. Tumor specimens were obtained during diagnostic procedures from patients with non-small-cell lung cancer which included bronchoscopic guided endobronchial biopsy, transbronchial biopsy, pleural biopsy, cell block from the centrifuged deposits of malignant pleural fluid and CT or USG guided transthoracic biopsy of lung mass. Tumor specimens obtained during these diagnostic procedures, after pathological confirmation the paraffin-embedded

material was subjected for EGFR mutation analysis and ALK rearrangement detection by IHC.

Clinical and pathological variables:

Detailed clinical and pathological data for analysis was collected from the all the patients which included sex, age at diagnosis, patient address, presenting symptoms, examination findings, smoking status, radiological, bronchoscopic findings, TNM stage at the diagnosis and histopathologic type.

Analysis of EGFR mutation and ALK rearrangement:

All the specimens were investigated for EGFR mutation, in exon 18-21 of the tyrosine kinase domain, by polymerase chain reaction (PCR) and the direct DNA sequencing method. ALK rearrangement was assessed by Immunohistochemistry (IHC).

EGFR mutation analysis by Sanger's sequencing:

Patient Samples-Formalin fixed paraffin embedded tumor tissue blocks from patients of NSCLC. An H & E slide of the block is studied to ascertain the presence of adenocarcinoma component and tumor content. Samples that have more than 200 tumor cells and more than 30% tumor content are processed for Mutation analysis using Sanger's sequencing. DNA is extracted from the sample using Proteinase K digestion followed by silica cartridge isolation procedure using QiaAMP DNA FFPE Tissue kit (Qiagen) as per manufacturer's instructions. DNA is quantitated using Nanodrop (Thermo Scientific) and its quality is ascertained by resolving on a 0.8% TBE Gel. Purified sample is stored at –80°C till further processing.

PCR, Sequencing and Analysis-The purified genomic DNA is amplified in four separate PCR reactions targeted at amplification of Exons 18, 19, 20 and 21 of EGFR gene. The placement of the Primers is such that it ensured amplification of the complete exons. Briefly, for each reaction 20-50ng of DNA is taken in a 0.2ml PCR tube. To this is added, 200nM each of Forward primer and Reverse primer and 12.5ul of 2X Phusion Flash Master Mix (Finnzyme), in a total reaction volume of 25ul. After an initial denaturation at 98°C for 3min, the PCR is run for 40 cycles at conditions: 98°C for 1min; 62°C for 1min; 72°C for 1min followed by a final extension at 72°C for 5min. The amplicon is resolved on a 3% gel to check the specificity of amplification. The product is purified using AxyPrep PCR cleanup Kit supplied by Axygen as per the manufacturer's instructions. Sequencing of PCR products

is carried out in both directions on ABI 3130xl Genetic Analyzer using standard chemistries. The sequences are compared against human genome sequence (NCBI accession NT_033962) using BLAST software to identify the mutations. The chromatograms are also analyzed manually using SeqScape v2.6 software.

Statistical analysis:

Data were analyzed using SPSS statistical software. The rates of EGFR mutation and ALK rearrangement between two groups were compared using the Chi-square Test. For all analyses, a p-value of P < 0.05 was taken as significant

RESULTS :

Patients’ characteristics:

A total of 100 patients were included in the study, of which 73 were Males and 27 were Females. The clinicopathologic features of the patients are summarized in Table 1. The median age at diagnosis was 58.86 (range 29-76) years old. Based on patients age two subgroups were made, those with age less than or equal to 60yrs (n=47 patients) and second group with age more than 60yrs (n=53 patients). The major presenting symptoms in decreasing frequency include cough, breathlessness, chest pain and hemoptysis. Among the 100 NSCLC patients enrolled in the study, 38 patients were never-smokers while 62 patients were current or ex-smokers (ever-smokers). The majority of patients had disease of clinical TNM stage III or IV. Among 100 NSCLC patients enrolled in the study, Adenocarcinoma histology was seen in 57 patients and Squamous cell type in 43 patients.

EGFR mutation and clinicopathological features :

We examined the EGFR mutation status in 100 cases of NSCLCs and found mutations in 19 cases (19%). EGFR mutation analyses were limited to the four exons (exons 18-21). Among the 19 patients harbouring EGFR mutation 3 patients showed mutation in Exon 21, rest all patients had mutations in Exon 19.

We analyzed the relationship between the EGFR mutation status and clinicopathologic factors in patients with NSCLC, summarised in table 2. After the statistical analysis of the two

subgroups it was found that EGFR mutations were significantly higher in adenocarcinoma (p < 0.001), never smokers (p= 0.001), and in younger age group with age less than or equal to 60yrs (p=0.002) in NSCLCs. EGFR mutations were present more frequently in females (8 out of 27 patients) as compared to males (11 out of 73 patients), though not statistically significant. Among the different presenting symptoms EGFR mutation was found to be more significantly associated with breathlessness.

ALK gene rearrangement and clinicopathological features :

Table 1: Shows the demographic data of the patients.

	No.	EGFR mutation (%)	ALK by IHC (%)
Total	100	19(19%)	2(2%)
Age			
<=60yrs	53	16	1
>60yrs	47	3	1
Sex			
Male	73	11	1
Female	27	8	1
Symptoms			
Hemoptysis	36	8	0
Cough	79	15	1
Chest pain	49	12	2
Breathlessness	66	8	1
Histology			
Adenocarcinoma	57	18	2
Squamous Cell Carcinoma	43	1	0
Smoking Status			
Ever smokers	57	3	0
Never smokers	43	16	2

Table 2: Shows the relation between clinicopathologic features Patient and EGFR mutation.

		EGFR MUTATION				total	Chi square	p value
		ABSENT		PRESENT				
		Count	%	Count	%			
AGE	<=60 Years	37	69.8	16	30.2	53	9.173	<u>0.002</u>
	>60 Years	44	93.6	3	6.4	47		
GENDER	FEMALE	19	70.4	8	29.6	27	2.715	0.099
	MALE	62	84.9	11	15.1	73		
COUGH	ABSENT	17	81.2	4	18.8	21	0	0.995
	PRESENT	64	81.1	15	18.9	79		
HEMOPTYSIS	ABSENT	56	83.6	11	16.4	67	0.88	0.348
	PRESENT	25	75.8	8	24.2	33		
CHEST PAIN	ABSENT	44	86.3	7	13.7	51	1.881	0.17
	PRESENT	37	75.5	12	24.5	49		
BREATHLESSNESS	ABSENT	23	67.6	11	32.4	34	5.968	<u>0.015</u>
	PRESENT	58	87.9	8	12.1	66		
TYPE OF CANCER	ADENOCARCINOMA	39	68.4	18	31.6	57	13.629	<u><0.001</u>
	SQUAMOUS CELL CARCINOMA	42	97.7	1	2.3	43		
SMOKING	NON SMOKER	27	62.8	16	37.2	43	16.253	<u><0.001</u>
	SMOKER	54	94.7	3	5.3	57		

Among the 100 NSCLC patients subjected to ALK gene rearrangement study by Immunohistochemistry (IHC), ALK gene rearrangement was found in only two (2%) patients, of either gender both with adenocarcinoma histology. Both these patients were non smokers, summarised in table 3.

DISCUSSION :

Table 3: Shows the relation between clinicopathologic features Patient and ALK gene rearrangement.

		ALK				total	Chi square	p value
		ABSENT		PRESENT				
		Count	Column N %	Count	Column N %			
AGE	<=60 Years	51	52.0%	2	100.0%	53	1.81	0.179
	>60 Years	47	48.0%	0	0.0%	47		
GENDER	FEMALE	26	26.5%	1	50.0%	27	0.548	0.459
	MALE	72	73.5%	1	50.0%	73		
COUGH	ABSENT	21	21.4%	0	0.0%	21	0.542	0.461
	PRESENT	77	78.6%	2	100.0%	79		
HEMOPTYSIS	ABSENT	65	66.3%	2	100.0%	67	1.005	0.316
	PRESENT	33	33.7%	0	0.0%	33		
CHEST PAIN	ABSENT	51	52.0%	0	0.0%	51	2.124	0.145
	PRESENT	47	48.0%	2	100.0%	49		
BREATHLESSNESS	ABSENT	33	33.7%	1	50.0%	34	0.233	0.629
	PRESENT	65	66.3%	1	50.0%	66		
TYPE OF CANCER	ADENOCARCINOMA	55	56.1%	2	100.0%	57	1.54	0.215
	SQUAMOUS CELL CARCINOMA	43	43.9%	0	0.0%	43		
SMOKING	NON SMOKER	41	41.8%	2	100.0%	43	2.705	0.1
	SMOKER	57	58.2%	0	0.0%	57		

In this study, we searched EGFR mutations, ALK gene rearrangement and explored the relationship between EGFR mutational status and clinicopathologic features in NSCLCs. The prevalence of EGFR mutations and ALK gene rearrangements was 19% and 2%, respectively. The prevalence of EGFR mutations in India as reported by various studies ranges from 16-40%.¹⁷⁻²⁰ In our study cohort, EGFR mutations were limited to the two exons (exons 19, and 21) of the TK domain. Since the discovery of EGFR mutations, they have been shown to be associated with specific clinicopathological characteristics namely female sex, never smokers, and adenocarcinoma histology. Previous studies indicated that adenocarcinoma histology, never smoker status, and female gender were factors associated with EGFR mutations.^{12,21-22} Similarly the

frequency of EGFR mutations in this study was observed to be significantly higher in patients with adenocarcinoma histology, never smokers and in younger age group. In our study cohort though the occurrence of EGFR mutations more frequently seen in females with NSCLC as compared to males, it was not statistically significant.

The EML4-ALK translocation defines a new molecular subset of NSCLC with distinct clinical and

pathologic features. The frequency of E M L 4 - A L K reported by previous studies ranges from 1.5% to 6.7%.^{15,23-27} previous reports observed that ALK gene rearrangement was more frequently associated with adenocarcinoma histology, tend to occur in light (d 10 pack years) or never smokers and in younger age group. There was no gender predilection.²⁸ In our study population of

100 NSCLC the frequency of ALK gene rearrangement was 2%. Both were of adenocarcinoma histology, non smokers and belonged to either gender.

In conclusion, this was the first study of its kind in North east region. In consistent with previous studies the frequency of EGFR mutations (19%) and ALK rearrangement (2%) was similar in patients with NSCLC in North-east region.

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Thyroid Dysfunction in Rheumatoid Arthritis

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Abstract

Introduction : Rheumatoid arthritis (RA) is a chronic inflammatory, multisystem and progressive disease characterized by a symmetric involvement of peripheral joints. It results in a variety of extra-articular manifestations including fatigue, subcutaneous nodule, lung involvement, pericarditis, peripheral neuropathy, vasculitis, thyroid and hematologic abnormalities. **Materials and methods:** The study sample comprised of 96 rheumatoid arthritis patients were being selected randomly who had attended Medicine department (O.P.D./Ward) and Rheumatology O.P.D. Gauhati Medical College and Hospital over period of 1 year and fulfilled the 2010 ACR:EULAR Classification Criteria. The patients were evaluated with detailed history, thorough clinical examination and appropriate investigations as protocol. **Results and Observations:** Thyroid dysfunction was present in 16.66% of RA patients and it is found to be more common in females than males. Clinical hypothyroidism was most common thyroid dysfunction present in 8 (8.33%) patients followed by subclinical hypothyroidism in 7 (7.29%) and hyperthyroidism in 1(1.04%) patients. **Conclusion:** From our study it can be concluded that thyroid dysfunction are common in RA patients. It is more common in females than in males. Clinical hypothyroidism is the most common thyroid dysfunction followed by subclinical hypothyroidism and hyperthyroidism in RA patients. Thyroid involvement is directly proportional to the disease duration, higher ESR value and higher CRP value but is unrelated to tender and swollen joint count and rheumatoid factor status.

KEYWORDS: *rheumatoid arthritis (RA), C reactive protein (CRP)*

INTRODUCTION :

Rheumatoid arthritis (RA) is a chronic inflammatory, multisystem and progressive disease characterized by a symmetric involvement of peripheral joints. Rheumatoid arthritis may result in a variety of extra articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, thyroid and hematologic abnormalities¹. The relationship between thyroid dysfunction and RA has been a subject of debate, where several surveys suggested a relation between Hashimoto's thyroiditis and RA.

The most common thyroid dysfunction was hypothyroidism, which was found in 24% RA patients, followed by subclinical hypothyroidism in 4% patients; whereas subclinical hyperthyroidism was present in 1.3% patients. Autoimmune thyroid disease was present in 6.6%

patients². There is a worldwide prevalence of autoimmune thyroid disease (AITD) in RA that varies considerably, ranging from 0.5% in Morocco to 27% in Slovakia. AITD is not uncommon in RA patients³. This study aims to document the clinical profile of thyroid dysfunction in patients suffering from rheumatoid arthritis and to correlate thyroid dysfunction with duration and severity of rheumatoid arthritis.

AIM AND OBJECTIVE :

1. To study the clinical profile of rheumatoid arthritis.
2. To study the profile of thyroid disease in patients with rheumatoid arthritis.

MATERIALS AND METHODS :

Hospital based observational, descriptive study was undertaken in the Department of Medicine, Gauhati Medical College & Hospital, Guwahati, Assam from 1st July 2015 – 30th June 2016. The study sample comprised of 96 rheumatoid arthritis patients selected randomly who had attended Medicine department (O.P.D./Ward) and Rheumatology O.P.D. and fulfilled the 2010 ACR:EULAR Classification Criteria. All the cases were subjected to a thorough history, clinical examination and relevant

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investigations. All patients underwent thyroid function testing for thyroid assessment.

RESULTS AND OBSERVATIONS :

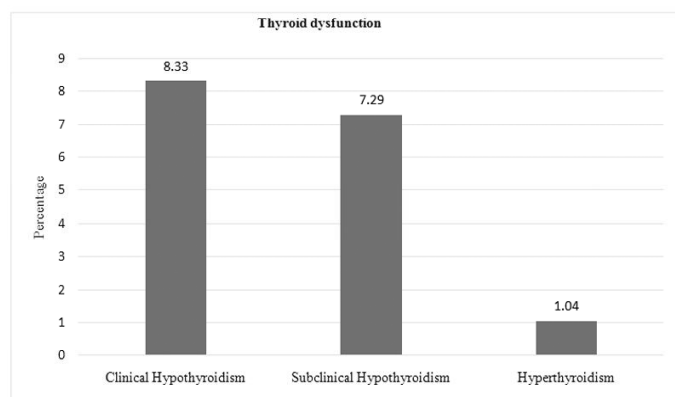
Thyroid dysfunction was present in 16 (16.66%) of RA patients and it is found to be more common in females than males. Clinical hypothyroidism was most common thyroid dysfunction present in 8 (8.33%) patients followed by subclinical hypothyroidism in 7 (7.29%) and hyperthyroidism in 1(1.04%) patients. (Table 1)

Table 1: Thyroid dysfunction in Rheumatoid Arthritis patients

Thyroid abnormality	Number of patients	Percentage
Clinical Hypothyroidism	8	8.33
Subclinical Hypothyroidism	7	7.29
Hyperthyroidism	1	1.04
Total	16	16.66

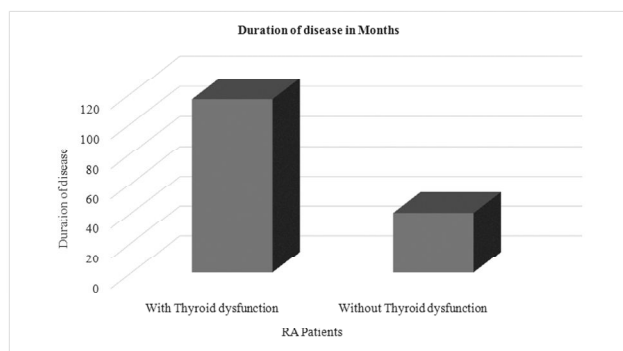
Figure 1: Bar diagram showing Thyroid dysfunction in RA patients.

Figure 1: Bar diagram showing Thyroid dysfunction in RA patients



In our study, the mean duration of disease in RA patients was 53.09 months (4.42 years) and the mean duration of disease in patients with thyroid dysfunction was 115.82 months (9.65 years) and in those without thyroid dysfunction was 39.87 months (3.32years). (Fig.2)

Figure 2: Bar diagram showing relation of Duration of disease to RA patients with Thyroid dysfunction and without Thyroid dysfunction



High ESR (>30) was found in 12 (75%) cases in RA with thyroid dysfunction group while in RA without thyroid dysfunction group it was in 45 (56.25%) cases (p<0.05). (Table 2)

Table 2: Relation of ESR to RA patients with Thyroid dysfunction and without Thyroid dysfunction

ESR	RA patients		Total	P Value	Mean of ESR
	With Thyroid dysfunction	Without Thyroid dysfunction			
High (>30)	12(75%)	45(56.25%)	57	<0.05	35.82
Normal (0-30)	4 (25%)	35(43.75%)	39		
Total	16 (100%)	80 (100%)	96		

CRP was high in 87.5 % of RA patients with thyroid dysfunction while in only 62.5% of RA patients without thyroid dysfunction, (p<0.05) (Table 3)

Table 3:Relation of CRP to RA patients with Thyroid dysfunction and without Thyroid dysfunction

CRP	RA patients		Total (N= 96)	P Value	Mean of CRP
	With Thyroid dysfunction (N=16)	Without Thyroid dysfunction (N=80)			
High(>10)	14 (87.5%)	50(62.5%)	64	<0.05	28.33
Normal(≤10)	2 (12.5%)	30 (37.5%)	32		
Total	16 (100%)	80 (100%)	96		

DISCUSSION:

In our study out of 96 study subjects 24 patients (25%) were male and 74 patients (75%) were female with a female to male ratio of 3:1 and include patients between 13 years to 72 years of age with a mean age of 44 years. Dasgupta S et al (2007)⁴ and Bhattacharya AK et al (2009)⁵ found a female to male ratio of 3:1 and 3.3:1 respectively. So our study is similar to both these studies.

Patients with thyroid dysfunction had 1 (6.25%) male and 15 (93.75%) females and those without thyroid dysfunction had 23(28.75%) males and 57 (71.25%) females. It shows that females are more likely to develop thyroid disease than males in RA. Shiroky et al (1993) showed thyroid dysfunction was seen at least three times more often in women⁶. So our study is well comparable to the above study.

Our study, of the 96 RA patients studied thyroid dysfunction was present in 16 (16.66%) RA patients. El-Sherif et al (2004) found the thyroid dysfunction in 15% of patients⁷. In another study Haghghi (2009) found the prevalence of 19.83% in RA patients⁸. So our study is well comparable to the above studies.

Clinical hypothyroidism was most common disorder present in 8 (8.33%) patients, followed by subclinical hypothyroidism in 7 (7.29%) and hyperthyroidism in 1 (1.04%) patients. Al-Awadhi et al (2008)⁹, Haghghi (2009)⁸ and Raterman et al (2008)¹⁰ shows that clinical hypothyroidism present in 10.2%, 8% and 6.8% patients respectively. This is comparable to the present study. Subclinical hypothyroidism was present in 7.29% of RA patients which was comparable to the Al-Awadhi et al (2008)⁹, Haghghi (2009)⁸, Mobini et al (2011)¹¹, El-Sherif et al (2004)⁷ and Przygodzka et al (2009)¹² studies who found similar results in 10.2%, 10.7%, 6.3%, 10% and 7% of RA patients respectively. Hyperthyroidism was reported in 1.04% patients similar to the Haghghi (2009) study which was in 1.13% of patients. So our study is well comparable to the above studies.

In our study, the mean duration of disease in RA patients was 53.09 months (4.42 years) and mean duration of disease in patients with thyroid dysfunction was 115.82 months (9.65 years) and those patients without thyroid dysfunction was 39.87 months (3.32 years). So high disease duration is associated with significant thyroid dysfunction in RA patients and this is statistically highly significant ($p < 0.05$). Elattar et al (2014) and Shiroky et al (1993) reported the mean duration of disease in patients with thyroid dysfunction of 9.8 years and 8.6 years respectively^{2,6}. Elattar et al (2014) also found the mean disease duration in patients without thyroid dysfunction of 3.2 years. So the present study is well comparable to the above studies.

In our study ESR was high in 75 % of RA patients with thyroid dysfunction. So high ESR was associated with thyroid dysfunction in RA patients. This is also statistically significant ($p < 0.05$). Elattar et al (2014)² found increased ESR is associated with significant thyroid involvement which is comparable to the present study.

In our study CRP was high in 87.5 % of RA patients with thyroid dysfunction. So high CRP was associated with thyroid dysfunction in RA patients and is found statistically significant ($p < 0.05$). Elattar et al (2014)² found high CRP is associated with increased risk of thyroid dysfunction in RA patients and present study is well comparable to the above study.

CONCLUSION:

In the present study, it was observed that Rheumatoid

arthritis affects females more than males. Maximum patients are presented with polyarthritis followed by early morning stiffness, constitutional symptoms, joint deformity, eye symptoms and subcutaneous nodules. Clinical hypothyroidism is the most common thyroid dysfunction followed by subclinical hypothyroidism and hyperthyroidism in RA patients. Females are more commonly affected than males. Thyroid involvement is directly proportional to the disease duration, higher ESR value and higher CRP value but is unrelated to tender and swollen joint count and rheumatoid factor status.

However a prospective study with larger sample size is required to arrive at the definite conclusion regarding association of thyroid dysfunction in RA patients.

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Etiological and Clinical Profile of Patients Presenting with Hemoptysis in A Tertiary Care Teaching Hospital in North Eastern India

D Das*, K Bhattacharjee**, C P Thakur***

Abstract

Background : Hemoptysis, an important and alarming symptom, often indicates serious underlying disease. A major problem in managing hemoptysis is the wider spectrum of causative factors. The effective management of hemoptysis depends upon identification of the etiology. The main aim of this study was to depict common etiological factors and patterns of its presentation and to compare it with that of rest of the world. **Materials and Methods :** A single centered prospective observational study was carried out on consecutive patients presented with hemoptysis in a tertiary care teaching hospital of north-eastern India, for a period of 8 months from 1st August 2016 to 31st March, 2017. **Results and Observations:** A total of 100 patients were included in the study out of which 63 were males and 37 were females, with a mean age of 48.5 years. Majority of the patients were non-smokers (46%). Pulmonary tuberculosis, bronchogenic carcinoma, bronchiectasis and idiopathic cases were found in 34%, 17%, 14% and 22% cases respectively. Majority of patients with Tuberculosis (81.25%) and lung mass (70.58%) had mild hemoptysis. Massive hemoptysis had poor outcome. More than half of malignancy cases had a normal chest -X-Ray. **Conclusion :** Hemoptysis is one of the alarming features of serious underlying disease. Tuberculosis is still the leading cause in developing countries like India followed by malignancy.

KEY WORDS : Hemoptysis; Tuberculosis; Bronchogenic carcinoma; Bronchiectasis.

INTRODUCTION :

The term 'hemoptysis' originated from the Greek 'haima' which means 'blood' and 'ptysis' which means 'a spitting'. Hemoptysis is defined as the expectoration of blood, caused by bleeding from the lung parenchyma or the tracheobronchial tree¹. The material produced varies from blood-tinged sputum to virtually pure blood. Hemoptysis, an important and alarming symptom, often indicates serious underlying disease. Its appearance induces concern to the patient and requires a full diagnostic evaluation².

Expectoration of even relatively small amount of blood is an alarming symptom and can be an indication for potentially dangerous disease like bronchogenic carcinoma. Massive hemoptysis into airway is an imminent threat to life because it may cause asphyxiation as the tracheobronchial tree is flooded with blood. Therefore the presence of hemoptysis of any degree always requires

thorough evaluation.³ The etiologies of hemoptysis varies from country to country and in different regions.

There is paucity of reports from north eastern part of India regarding etiological factors of hemoptysis and therefore a humble attempt was made to find out the common clinical profile and etiological factors in patients presenting with hemoptysis and to compare it's finding with that of other areas of the world or country.

MATERIALS AND METHODS :

A single centered prospective observational study was carried out on consecutive patients presented with hemoptysis in a tertiary care teaching hospital in north eastern India for a period of 8 months from 1st August 2016 to 31st March, 2017. Total of 100 patients complaining of hemoptysis were taken up for the study. All the patients were admitted to hospital for further evaluation. The study was approved by the institutional ethical committee and informed consent from all patients was obtained prior to enrollment into the study.

Detailed clinical history was recorded and thorough physical examination was done and was recorded in preformed proforma.

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The quantity of hemoptysis was estimated from the patient's history, and was classified arbitrarily according to the severity into mild (<30ml/day), moderate (30-200ml/day) or severe (>200ml/day) depending upon the amount of bleeding.

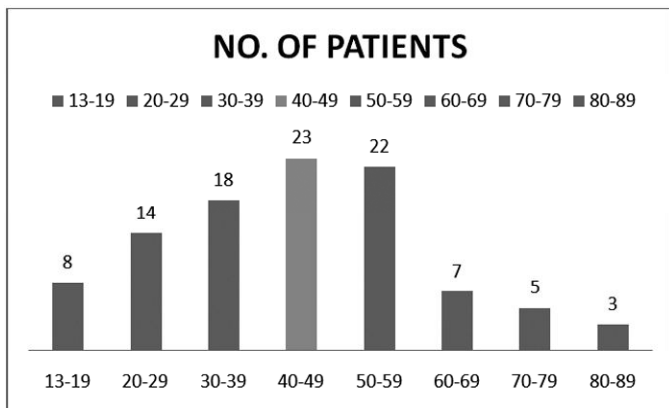
On admission routine investigations were performed including complete hemogram, liver function tests, Serum(S) creatinine, S. Blood sugar, S. electrolytes, Routine urine examination, chest radiograph PA view, sputum examination for acid fast bacilli(AFB), coagulation profile when indicated, Anti GBM antibody in selected cases, Aspergillus antigen test, Echocardiography in selected cases etc. ENT examination was carried out in doubtful cases to rule out upper respiratory tract bleed. Bronchoscopy was carried out in selected cases and Bronchial lavage was sent for routine culture and staining for acid-fast bacillus and cytology for malignant cells. Transbronchial or endo- bronchial biopsies were done in relevant cases where necessary. HRCT or CECT thorax was also performed as and when indicated. The etiology of hemoptysis was determined on the basis of all available clinical data, investigation findings including CT scan thorax, and bronchoscopic findings.

Data collected was analyzed using Microsoft Excel. Statistical analysis was done using Chi- Square test & p value <0.05 was taken as statistically significant.

RESULTS & OBSERVATIONS :

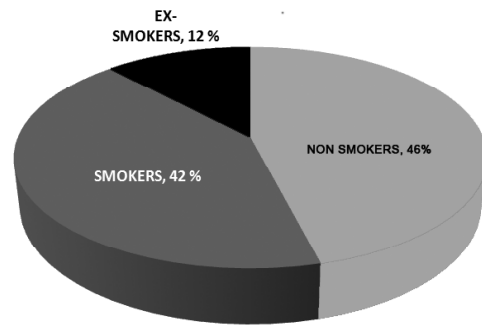
In the present study, out of total 100 patients 63 were males and 37 were females, the male-female ratio being 1.7:1. The age range of the cases varied from 16 to 86 years with mean age of 48.5 years. The age distribution was as follows:

Fig 1: Distribution of Number of Patients According to Age Groups



Maximum cases were seen in the age group 40 to 49 years (23 cases), closely followed by the age group 50 to 59 years (22 cases). Only 3 cases were seen between 80 to 89 years.

Fig 2: Distribution of Patients According to Smoking Habits

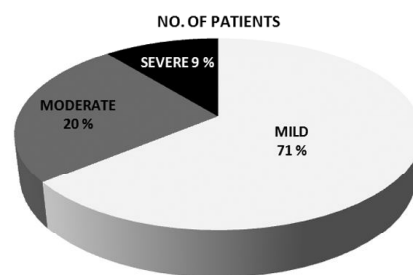


In the present study majority of the patients were non-smokers (46%). 12% of the patients were not smoking or taking any tobacco products since last 6 months.

In 77% of patients this was the first episode of hemoptysis, while 23% patients already had previous episodes.

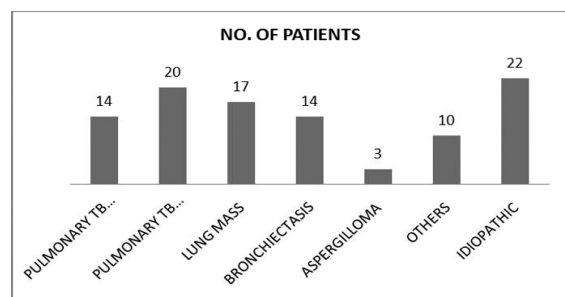
Majority of the patients (71%) had mild hemoptysis while moderate hemoptysis was present in 20% of patients and only nine patients (9%) had severe hemoptysis.

Fig 3: Distribution of Patients According to Severity of Hemoptysis



Etiologies of severe hemoptysis were active pulmonary tuberculosis, lung cancer, aspergilloma, and Bronchiectasis.

Fig 4: Distribution of Patients According to Etiology



In the present study, Tuberculosis was the most common etiology of hemoptysis in 34% cases followed by malignancy in 17% and bronchiectasis in 14%. Among the patients with Tuberculosis, 14% of the patients had active pulmonary tuberculosis while 20% of the patients had old pulmonary tuberculosis. In 22% of the patients even after doing all the routine blood investigations, chest X-Ray & CT chest, the exact cause of hemoptysis couldn't be determined. In other 10% cases, causes of hemoptysis were Pneumonia (2 cases), acute myeloid leukemia (2 cases), mitral stenosis (2 cases), lung abscess (1 case), systemic sclerosis (1 case), warfarin induced (1 case), pulmonary embolism (1 case).

Table 1: Distribution of Patients According to Volume of Hemoptysis

CAUSES	MILD	MODERATE	SEVERE	TOTAL
PULMONARY TB	26 (76.4%)	5 (14.8%)	3 (8.8%)	34
BRONCHIECTASIS	10 (71.4%)	3 (21.4%)	1 (7.20%)	14
LUNG MASS	12 (70.6%)	3 (17.6%)	2 (11.8%)	17
IDIOPATHIC	16 (72.7%)	5 (22.7%)	1 (4.6%)	22
ASPERGILLOMA	0	1 (33.3%)	2 (66.7%)	3
OTHERS	7 (70%)	3 (30%)	0	10
TOTAL	71	20	9	100

In the present study, majority of patients with Tuberculosis (76.4%) and lung mass (70.6%) had mild hemoptysis. In the patients of hemoptysis with idiopathic origin, 16 patients (72.7%) had mild hemoptysis. Of the 20 patients with moderate hemoptysis, 25% patients were diagnosed as tuberculosis and in equal number of patients (25%) the etiology for hemoptysis was not found. Active pulmonary tuberculosis, lung mass & aspergilloma were the common causes of severe hemoptysis, followed by 1 case each of Bronchiectasis and idiopathic hemoptysis. Mild to Moderate hemoptysis had a good prognosis. Massive hemoptysis had poor outcome. 6 (66.66%) out of 9 patients with severe hemoptysis died.

Table 2: Distribution of Patients According to Diagnostic Evaluation

	NORMAL	ABNORMAL	P value
CHEST X RAY	32	68	<.001
CT CHEST	7	70	<.05
BRONCHOSCOPY	1	4	<.05

Chest radiography was performed in all cases, out of which 68 (68%) cases had abnormal radiograph and remaining 32% had normal radiographs. 77 patients underwent CT scan chest, of which 7 had normal report. Bronchoscopy was performed in only 5 patients in whom it showed abnormality in 2 cases each of bronchiectasis

& lung mass. In remaining 17 patients out of 22 cases of idiopathic hemoptysis bronchoscopy couldn't be done due to various reasons. All 22 cases of idiopathic origin had normal chest X-Ray. 10 out of 17 malignancy cases (58.82%) had a normal chest X-Ray. Among patients with lung cancer, CT scan had a good diagnostic yield (100%).

DISCUSSION :

Hemoptysis is common and potentially serious condition in all parts of the world including India. The causes of hemoptysis vary in different literature and in different parts of the world. In developing countries including India, tuberculosis still remains the most common cause of Hemoptysis.^{4,5,6}

Pulmonary tuberculosis was the most common cause of hemoptysis four decades ago as shown by Rao in his study in 1960,⁷ and it is still the leading cause of it as is evident from this study, in which tuberculosis was found in 34% of patients with hemoptysis and in another recent study K. R. Patel et al¹⁸ in which tuberculosis was found in 60% of patients and also in Kumar A et al¹⁹ in which Tuberculosis was in 40% of patients. Various studies from other developing countries have also shown pulmonary tuberculosis to be the major cause of hemoptysis.^{8,16,17} Recent studies showed a change in the trend in causes of hemoptysis in which incidence of tuberculosis is decreasing as compared to previous studies.^{9,10,11,12} The decrease in the incidence of tuberculosis can be attributed to increase awareness, improved diagnostic technique, quality medication & Revised National Tuberculosis Control Program (RNTCP).

Of all the patients in the present study, second most common cause of hemoptysis cases was malignancy in 17% followed by bronchiectasis in 14%. Many other studies like Abott et al, Moersh et al, Santiago et al & Fidanet al^{4,5,13,14} has shown malignancy to be among the most common causes. But there are many older studies which have not shown malignancy to be that common¹⁵. The reason probably was the unavailability of better diagnostic modalities like CT scan and bronchoscopy, and malignancy probably remained in the idiopathic category. We observed that the patients with malignancy most of the times had mild hemoptysis which is true for other studies as well.^{15,16,18}

Hemoptysis was commonly (23%) found in the age group 40-49 years, followed by 50-59 years age group (22%). Male female ratio in the present study was found to be 1.7:1, concluding males are more susceptible to develop hemoptysis than females. Abal et al¹ found it 4.2 times more common in males than in females. The findings of the present study were very similar to those found by Fidan et al¹⁴ (2.72:1).

Smoking is also considered important risk factor in the development of hemoptysis. But majority of the patients (46%) were non smoker in the present study in contrast to Abal et al & Subodh et al^{1,16}. Majority of the patients (91%) in the present study was presented with mild to moderate hemoptysis and only 9% of patients had severe hemoptysis similar to K.R.Patel et al.¹⁸

The main limitation of our study is that the study was carried out on a very little number of patients that may or may not represent the community.

CONCLUSION :

Hemoptysis is the early but dangerous symptom of underlying disease and should not be ignored. Even one episode of hemoptysis needs a meticulous workup and thorough investigation. We conclude that pulmonary tuberculosis remains the most common cause of hemoptysis in this part of the country. Hemoptysis even if mild should be extensively evaluated as malignancy is the second most common cause in our setting. A normal CXR does not rule out lethal causes of hemoptysis. CT Thorax & Bronchoscopy are helpful in such setting. Patients older than 50 years with a positive smoking history need an extensive evaluation and follow-up to exclude lung carcinoma.

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A Tale of Emerging and Re-emerging Infections – An Indian Perspective

B K Das*, N Das**

*“It was the best of times, it was the worst of times,
it was the age of wisdom, it was the age of foolishness,
it was the epoch of belief, it was the epoch of incredulity,
it was the season of Light, it was the season of Darkness,
it was the spring of hope, it was the winter of despair...”*

Charles Dickens

We live in a world that had been so aptly described by Charles Dickens years ago in his famous novel entitled “A tale of two cities”. All the advances of the modern world, however, taken a heavy toll not only on the humans but also on all living beings. In the last many decades the rapid progress in technology in travel, urbanization, agriculture, farming and commercial activities have caused changes in our ecosystem and the ways we live. These changes sometimes alter the fundamentals of life compelling only the survival of the fittest. With increasing industrialization, the compulsion to trade with other nations have tremendously increased travel to all corners of the world transporting not only goods but also large number pathogenic microbes as well as their vectors resulting in adaptation of these organisms to newer environment and quick spread among immunologically naïve populations (Table 1). This process of evolution for the microbes is repeated many times over posing great threats to the masses of acquiring newer infectious diseases. With the availability of newer drugs to fight microbes, antibiotic resistant bugs e.g. MRSA, VRE, drug resistant Salmonella, MDR/XDR TB have become a common phenomenon worldwide. Climatic changes due to global warming have

Table 1 : Factors contributing to emergence and re-emergence of Infectious Diseases worldwide

Factors	Mechanism	Examples of Infectious Disease
Globalization	Travel and trade	Influenza, Dengue, SARS, HIV, TB, Chikungunya, Malaria
Demographic Changes	Mass migration/ Civil War, Earth quake Flood, Hurricane	Cholera, Chikungunya Leptospira, E. coli, Shigella
Poverty & Social inequality	Hygiene, poor nutrition lack of safe water, overcrowding	Cholera, Influenza, Malaria, parasites
Agricultural Practice	Pig farming, Chicken & Goose Farming, Animal and plant feed with antibiotics, antifungals	H5N1, H1N1, Nipah, Hantavirus drug resistant salmonella, drug resistant Aspergillus
Environmental Global warming	Climate Change (El nino) Dam building	Spread of Cholera to South America via warm ocean current, S, mansonii in Upper Egypt, Malaria, Dengue
Deforestation Rapid Urbanization	Increase contact with animals, Vector population	Dengue, Chikungunya, Ebola, Nipah
Agent	Evolution of microbes, Mutations, crossing species barrier, adapting to new vector drug resistance newer route of transmission	HIV, Monkey Pox, Chikungunya MERS Corona virus, Rotavirus Crimean Congo Haemorrhagic fever MRSA, drug resistant malaria Ebola
Vector	Adaptation to newer environment Increased population, pesticide resistance	Aedes albopictus spreading Chikungunya in North America (a temperate climate) Scrub typhus, Plague, Leishmania
Host	Sexual, drug abuse Outdoor activity	HIV, Syphilis, Drug resistant gonorrhoea Scrub typhus, Leishmaniasis
Bioterrorism Threat	Aerosol dissemination	Anthrax, Plague, Small Pox, Tularemia
Breakdown of Public health Measures	Failure of vector control, Decrease in Chlorination of water, inadequate vaccination, Lack of political will	Malaria, Cryptosporidium, Diphtheria, SARS in China

played havoc in the environment resulting in EL Nino, hurricanes and flooding in many parts of the world creating situation for amplification of unusual pathogens like leptospira, Cholera vibrio and other vector borne pathogens. Failure of public health measures like vector control, lack of renewed pesticide programmes, inadequate vaccine coverage, lack of political will greatly influence the process of emergence or re-emergence of infectious diseases worldwide.

In the last fifty to sixty years the world has seen a massive rise in epidemic of infectious diseases like Smallpox (since eradicated), HIV, Influenza (H5N1 &

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H1N1), SARS, MERS, Cholera (O1 & O139), drug resistant Salmonellae, MDR tuberculosis/XDR tuberculosis, Plague etc. The rapid spread of these infectious diseases (as emerging or as re-emerging agents) can be attributed to multiple reasons (Table 1). Since a large proportions of rapidly spreading pathogens causing epidemic and pandemic diseases belong to viruses or prions, their nano morphology make it possible for transmission through aerosol (respiratory tract) or blood transfusion (viremia) or through water borne transmission or through sexual transmission e.g. Zika and Ebola^{1,2}. Increasingly a certain number of pathogens have adapted well to transmission through human to human contact avoiding use of vector or other amplifying host e.g. Ebola infection³. Interestingly some pathogens have adapted to alternate host/vector species for survival (Eastern Central South African genotype of Chikungunya virus with mutation of A226V of E1 protein, had adapted well in *Aedes albopictus* instead of *Aedes aegyptii*, causing explosive pandemic across many nations including North America^{4,5}.

The division between a rich and a poor nation had never been so wide in human civilization. The history of infectious disease is always full of incidence of majority of infectious diseases occurring predominantly in poor less developed countries where free health care, vaccination, public health surveillance programmes are either poor or almost nil in existence. In the last several decades India had its share of emerging and re-emerging infections with

O139 *Vibrio cholerae* causing massive outbreaks of cholera in 1992-1993 affecting mostly adults as well as children in Chennai and West Bengal which then slowly spread to other parts of India and subsequently became an endemic disease (Table 2)⁶. Plague outbreak of Surat in the year 1994 caused huge loss to exchequer to the tune of USD 1.7 billion with closure of almost all commercial activities coming to a halt⁷, the disease is endemic to certain parts of the country like Andhra Pradesh, Karnataka, Tamil Nadu, Himachal Pradesh and Uttarakhand because of existence of a sylvatic cycle⁸.

A recent outbreak of diphtheria caused by *Corynebacterium diphtheriae* in Assam, Kerala, Karnataka, Delhi is a cause of concern raising issues of inadequate immune coverage in young children. The last major outbreak of diphtheria was in 2000 in Delhi, mostly affected were younger children whereas the epidemiology of the recent outbreaks involved older children as well as adults^{9,10,11,12,13}. The 2017 outbreak of Diphtheria in Cox Bazar, Bangladesh among Rohingya refugees is a cause of worry for the Indian States of Assam, Tripura, Mizoram, Meghalaya and Manipur¹⁴. Occurrence of a large number of encephalitis in adult population in several parts of Bengal in 2001 lead to the identification of Nipah Virus (NiV) outbreak with a subsequent smaller outbreak in 2007, while neighbouring Bangladesh had reported several outbreaks till 2013¹⁵. Nipah virus infection is usually associated with pig farming in Malayasia, however, the Bengal and Bangladesh outbreaks identified a fruit bat (*Pteropus*) as the host, people acquired the infection drinking raw date palm sap that was contaminated by the fruit bat¹⁶.

Influenza virus, a segmented RNA virus caused massive pandemic disease worldwide affecting 500 million people with 10-20% mortality. It was the first influenza pandemic beginning in 1918¹⁷. The 8 segmented virus with Haemagglutinin (H) and Neuraminidase (N) evolved in different vertebrates including birds (avian) or pig (swine) where it mutates into virulent forms by recombination of different gene segments when multiple types of virus infect the same host e.g. H5N1-Avian Flu or H1N1 - Swine flu. India encountered swine flu in the states of Maharashtra and Gujarat in 2010

Table 2: Emerging and Re-emerging infections that pose major threat to public health in India

Disease	Location/Year of Incident
Plague	Surat (1994), HP (2002), Uttarakhand (2004)
Nipah Virus infection	Siliguri (2001)
Swine Flu (H1N1)	All most all states of India in 2004-2005, 2015-2018.
Avian Flu (H5N1)	Many states in 2006
Chikungunya	All most all states from 2003 onward
Dengue	Now endemic in almost all the states (1964 onward)
Chandipura	Andhra (2003), Gujarat (2004)
Crimean Congo Haemorrhagic Fever	Gujarat (2011)
Vibrio cholera O139	Chennai (1992), Bcngal (1993), many states endemic in many states
Diphtheria	Delhi (2000), Kerala (2016), Karnataka (2016), Assam (2016)
Leptospirosis	Mumbai (2005), Odisha (1999), Gujarat (2011), Chennai (2015)
Acute encephalitis syndrome (Scrub typhus)	Assam, UP, West Bengal, Odisha, Tamil Nadu, Karnataka, Manipur, Tripura, Mcghalaya, Sikkim (2010-2016)

affecting 23.4 % of a population of 1,54,259 tested¹⁸. Transmission of the virus is rapid and highly contagious as it spreads through droplet nuclei. Crimean Congo haemorrhagic fever (CCHF), a tickborn disease caused by Nairovirus was first reported from Gujarat in 2011, changes in the climatic condition may have increased the tick population for spread of the disease among risk population^{19,20}. Another tickborn disease Tick Typhus, caused by *Orientia tsutsugamushi* has been increasingly reported from various states of India with increasing association with Acute Encephalitis Syndrome in addition to causing typhus fever.^{21,26}

A case in point of emerging diseases is Chikungunya infection in India. Chikungunya fever caused by Chikungunya Virus (CHIKV) was first reported in Tanzania, Africa in 1956. African Chikungunya Virus circulates primarily in sylvatic/enzootic cycle transmitted by arboreal primatophilic *Aedes* mosquitoes. Of the three lineages of Chikungunya virus the West African genotype, the East/Central/South African genotype and the Asian genotype, the Asian genotype was responsible for the outbreak in India in 1963 and 1973.²⁷ The later outbreak of 2004-2007 was attributed to the East African genotype.²⁸ Currently almost all the states of India have reported the disease and it has become endemic in the Northern part of the country.

Dengue virus infection has traversed the length and breadth of the world, its presence is in more than 100 countries with occurrence of 50-100 million cases every year. Nearly 3.97 billion people from 128 countries are at risk²⁹. The disease has become rampant in many states of India including the Union Territories as well as Odisha, Assam, Arunchal Pradesh and Mizoram where the disease did not exist. The drastic increase of Dengue infections in India is mainly attributed to unplanned urbanization, environmental changes, inadequate vector control measures and spread of the disease to a immunologically naive population. The fact that the virus is transmitted by both *Aedes aegyptii*, and *Aedes albopictus* significantly increase the risk by many fold.

The changing profiles of the emerging and re-emerging infections in the context of globalization, climate changes, migrations mandate planning and implementation of preventive and control strategies both at International, National as well as local levels, as some these infectious

diseases have ability to cause pandemic (Table 3). The recent explosive outbreak of diphtheria cases in Cox bazaar, Bangladesh among Rohingya refugees from Burma, the containment of Ebola outbreak in West Africa or massive cholera outbreak in Yemen illustrate the point where International organization like World Health

Table 3: Organizations and Strategies involved in control and prevention of threat from emerging and reemerging diseases

<p>National Public Health Programmes under Government of India</p> <ul style="list-style-type: none"> • The Central Council of Health and Family Welfare (1995) • National Disease Surveillance & Response System (NAAC- 1996) • National Surveillance Programme on Communicable Diseases (NSPCD-1997) • Integrated Infectious Disease Surveillance (IDSP- 2004) • Rapid Response Team (RRT) • Food Surveillance System • Unofficial Sources • National Health Emergency Response system <p>International Organizations</p> <ul style="list-style-type: none"> • International Health Regulation (2005) • World Health Organization (WHO) <ul style="list-style-type: none"> ➤ Global Outbreak Alert and Response Network (GOARN) • Centre for Disease Control (USA).

Organization through its Global outbreak Alert and Response Network (GOARN), National Health Organizations as well as Non Governmental organization like Sans Frontiers play key roles. It is well understood that the political will of the Government to prevent and contain these infections are vital to the success of the programmes.

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Hemophagocytic Lymphohistiocytosis Secondary to Inflammatory Myopathy

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Abstract

We report a case of 16 year old boy who presented with fever, pancytopenia and swelling of face and all four limbs which proved to be due to inflammatory Myopathy. Investigations, including a bone marrow study, revealed hemophagocytic lymphohistiocytosis which was secondary to Myopathy. He responded to immune-suppressants initially but later had a relapse and succumbed.

INTRODUCTION :

Hemophagocytic lymphohistiocytosis is a rare but life threatening clinical syndrome characterised by exaggerated and ineffective immune response leading to a hyper inflammatory state.¹ The pathophysiology of HLH is postulated to be impaired activity of NK cell and cytotoxic T-cell associated with inflammatory signal defect leading to hypercytokinemia.² HLH can be classified as primary and secondary. Primary HLH is secondary to underlying genetic defect which include mutation in perforin gene or gene important for exocytosis. Acquired forms of HLH are associated with infections, autoimmune diseases and underlying malignancies.

Here we report a case of 16 year old boy with HLH secondary to inflammatory myopathy.

CASE REPORT :

A 16 year old boy presented to us with 2 months history of fever, swelling of both upper and lower limbs and face and progressive dyspnea since 15 days. On examination, he had tachycardia, tachypnea, temperature of 101.4°F. Patient was pale, had periorbital and facial puffiness, with bilateral symmetrical swelling of upper and lower limbs. Respiratory system examination revealed decreased breath sounds in

left infrascapular, infra axillary region, s/o left pleural effusion. Motor system could not be accessed accurately because of edema but power was decreased 3/5 proximally and 4/5 distally. Other systems were normal. Our initial clinical impression was inflammatory myopathy, left pleural effusion with anemia.

Investigations revealed: Hb : 9.6gm/dL (12 – 15), TC : 3390cells/mm³ (4000 – 11,000), PC : 1.16 Lcells/mm³ (1.5 – 4.0), PS : NCNC with leucopenia & thrombocytopenia, ESR: 15 mm/hr, LFT: Protein: 5.4gm/dl(6.0–8.2), Albumin : 2.4 gm/dl(3.4 - 5), Bilirubin: 0.43mg/dl(0.2 – 1.0) Direct: <0.05 mg/dl(0.0–0.2) AST: 586U/L(15–37) ALT: 412U/L(16–63) ALP: 121 U/L(46 - 116) GGT: 80 U/L(15 – 85) BU: 53 mg/dl (15 – 40) Cr: 0.7 mg/dl (0.6 – 1.13)

Serum Sodium: 133 meq/L (136–145)

Potassium: 3.9 meq/L (3.5 – 5.1)

Chloride: 100 meq/L (98 – 107)

RBS: 91mg/dl (< 140)

Fever work up which included blood and urine cultures; serologies: Widal, Weil Felix, leptospira IgM; viral markers: HIV, HbSAg, HCV, CMV IgM were negative.

CXR: Left pleural effusion. This was confirmed by CT- PNS and chest which showed moderate left pleural effusion with basal collapse with minimal right pleural effusion. Pleural fluid analysis showed lymphocyte predominant exudative pleural effusion with elevated ADA levels. Ultrasound abdomen showed fatty

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hepatomegaly. Connective tissue disorder was ruled out with negative ANA, p ANCA, c ANCA & ANA profile, normal C3 and C4 levels. CD4 count was low with 67 (410 – 1590). He was started on broad spectrum antibiotics and empirical ATT but showed no improvement and had worsening pancytopenia. Meanwhile we confirmed our diagnosis of inflammatory myopathy with elevated CPK: 4,488 U/L (male: 39 – 308), EMG and muscle biopsy.

Bone marrow biopsy done for evaluation of pancytopenia and fever revealed hemophagocytosis. Further work up for HLH was done which revealed hypofibrinogenemia: 138 (220-496), elevated ferritin: >16,500 ng/ml (23.9 -336.2) and hypertriglyceridemia: 1404 mg/dl. Perforin gene assay was negative and diagnosis of primary HLH was ruled out. This confirmed our diagnosis of hemophagocytic lymphohistiocytosis secondary to inflammatory myopathy.

He was initially treated with injection methylprednisolone, but since there was no improvement, he was given intravenous immunoglobulins and pulse therapy with cyclophosphamide. He improved wherein edema subsided, muscle power improved, pancytopenia recovered and liver function tests normalized.



Patient was discharged and on follow up CD 4 count was normal. He completed 4 cycles of monthly cyclophosphamide as an outpatient, but then had relapse of fever, went onto develop necrotizing pancreatitis and succumbed to its complications.

DISCUSSION :

Patients with HLH usually have a rapidly progressive fatal clinical course despite aggressive treatment. Diagnostic criteria for HLH must fulfill 5 out of the following 9 criteria.³

1) Fever 2) splenomegaly 3) cytopenias involving 2 or more cell lines 4) hypertriglyceridemia or hypofibrinogenemia 5) Hemophagocytosis on bone marrow 6) Hepatitis 7) Low/ absent NK cell activity. 8) Sr.Ferritin > 500 mg/dl 9) soluble CD 25 > 2400/ ml. In our patient six of the following criteria were fulfilled leading to a diagnosis of HLH.

Secondary HLH occurs most commonly in the setting of underlying infections including bacterial, viral, fungal and parasitic; malignancies like lymphoma, leukemia, carcinoma lung and liver and autoimmune diseases. Our patient had HLH secondary to inflammatory myopathy and initially improved with immunosuppressants. However, he had relapse of fever and pancytopenia, developed pancreatitis probably secondary to hypertriglyceridemia and succumbed to the illness.

CONCLUSION :

Inflammatory myopathy associated HLH is a rare entity and very few case reports are available in literature^{4,5,6,7}. Timely diagnosis of this immune dysregulatory disorder may be challenging because of the rarity of the syndrome, the variable clinical presentations, time required to perform diagnostic tests and lack of specificity of the clinical and laboratory findings. Most often the clinical picture can mimic a gram negative septicemia. Treatment is also complicated by dynamic clinical course, high risk of treatment related morbidity and disease recurrence.⁸

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CONSENT FORM FOR CASE REPORTS

For a patient's consent to publication of information about them in a journal or thesis

Name of person described in article or shown in photograph : _____

Subject matter of photograph or article : _____

Title of article : _____

Medical practitioner or corresponding author : _____

I _____ [insert full name] give my consent for this information about MYSELF OR MY CHILD OR WARD/MY RELATIVE [insert full name]: _____, relating to the subject matter above (“the Information”) to appear in a journal article, or to be used for the purpose of a thesis or presentation.

I understand the following :

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2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
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Small Cell Carcinoma of Oesophagus : A Rare Case Report from Upper Assam

G C Deka*, J Das*

Abstract

Small cell carcinomas (SCCs) are more often described in lungs, but rarely laryngeal, pancreatic, stomach, prostatic, uterine, sweet glands, and esophageal locations are reported. Esophageal and extrapulmonary small cell Carcinoma (EPSCC) was described first by McKeown in 1952. Primary small cell carcinoma (SCC) of the esophagus is a relatively rare malignancy, accounting for 0.05 – 4% of all esophageal malignancies. It is a highly aggressive tumor associated with a poor prognosis, similar to SCC that arises in the lung.

Endoscopic and radiological findings of PSCCE resemble squamous or adenocarcinoma of the esophagus. Definitive diagnosis of PSCCE is diagnosed by cytological examination with esophageal abrasive balloon and endoscopic punch biopsy. Treatments such as operation alone, local radiotherapy, chemotherapy alone or operation with adjuvant therapy have been reported. In the limited disease, after surgical resection, short-term results of chemotherapy and radiotherapy are good, although long-term results are still poor.

Case report: A 63 years old male patient was admitted in our ward with history of progressive dysphagia to solid and liquid for last two months along with history of significant unintentional weight loss. His **Upper G.I endoscopy showed** esophageal growth at 25 cm from upper incisor teeth, **Biopsy** suggestive of small cell carcinoma, **CECT thorax**: revealed gross circumferential thickening of esophagus with narrowing of the lumen from D6 to D9 levels with other biochemical parameters within normal limit. We treated the patient conservatively with chemo-radiation.]

KEYWORDS : *small cell carcinoma, immunohistochemical, tumor.*

INTRODUCTION:

Primary small cell carcinoma (SCC) of the esophagus is a relatively rare malignancy, accounting for 0.05 – 4% of all esophageal malignancies.¹ It is a highly aggressive tumor associated with a poor prognosis, similar to SCC that arises in the lung² and other extrapulmonary organs, including breast, ovary, uterine cervix, liver, salivary gland, stomach, colon, prostate, urinary bladder and kidney. Histologically, SCC is characterized by neuroendocrine-like architectural patterns, including nested and trabecular growth with common features including peripheral palisading and rosette formation in the tumors. Analogous to small cell lung cancer, diagnosis of esophageal SCC is aided by immunohistochemical staining for common neuroendocrine markers, including Syn, CgA and NSE. Recently, CD56 (neuronal cell adhesion molecule)

and TTF-1 (Thyroid Transcriptional Factor-1) were also reported to be high positivity in small cell carcinoma arising in different organs and thought to be useful markers for diagnosis of the tumor.

We are presenting here a case report of a small cell carcinoma of oesophagus as a rare oesophageal carcinoma which is probably the first case report published from north eastern (upper Assam) part of our country.

CASE REPORT :

A 63 years old male patient was admitted in our ward with history of progressive dysphagia to solid and liquid for last two months along with history of significant unintentional weight loss. He also complained of decreased appetite with pain abdomen and drooling of saliva with cough but without expectoration. He did not complain of fever, chest pain, jaundice, black colour stool, blood vomiting etc. He was neither a smoker nor alcoholic but chews betel nut occasionally. His bowel habits and micturition were normal with slight disturbances in sleep. He is a non-vegetarian and belongs to a lower middle class family. He gave no history of allergy to any ingested or inhaled.

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On examination :

The patient was conscious, cooperative, well oriented, mild pallor present. No icterus, clubbing, koilonychia, oedema, lymph gland present. He had mild rise of temperature and his respiration, pulse, blood pressure were within normal limit. His nervous system, cardiovascular system were normal. We found fine crepitation in right upper chest without any other significant abnormality in rest of the chest. His abdomen was mildly tender in the epigastrium without any hepatosplenomegaly or palpable lymph node.

Laboratory investigation :

Haemoglobin: 13gm/dl, TLC: 7900cc, ESR: 60mm 1st hour, Blood urea: 29mg/dl, s.creatinine: 1.1mg/dl, liver function test: normal, RBS: 88 mg/dl, S.Na+: 138mmol, S.K+: 3.9mmol, CXR-PA view= normal, USG whole abdomen= normal

Upper GI endoscopy: Revealed esophageal growth at 25 cm from upper incisor teeth (biopsy taken),

Biopsy: Tissues taken from the oesophageal growth shows malignant tumour composed of sheets of small round to oval cells with hyperchromatic nuclei and scanty cytoplasm suggestive of small cell carcinoma,

CECT thorax reveals gross circumferential thickening of esophagus with narrowing of the lumen from D6 to D9 levels associated with paraesophageal soft tissue element infiltrating into the mediastinal fat planes and around the descending aorta Lung parenchyma pleura, thoracic wall and other parts of mediastinum within normal limits.

We advised immunohistochemistry examination to the patient but due to financial constraint patient failed to follow it. We advised the patient to attend higher oncology centre

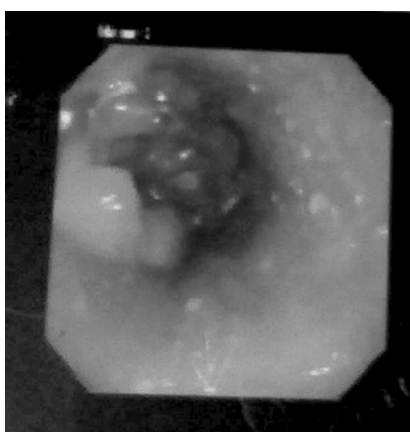


Fig.1. Oesophageal growth in upper part of the esophagus found on esophagogastroduodenoscopy

for further management but due to financial problem they wished to get treatment in our hospital. We treated the patient with chemo-radiation which was uneventful and patient was discharged with good health with advice to attend after one month.

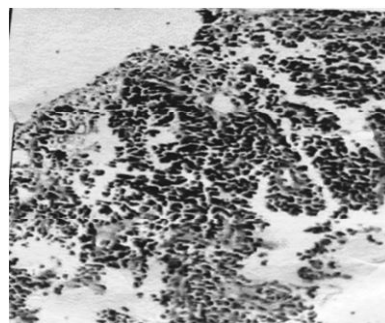


Fig.2. Histological findings of the tissues taken from the oesophageal growth

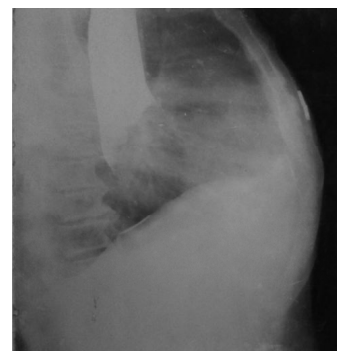


Fig 3. Barium swallow X-Ray of esophagus showing the filling defect



Fig.4. HRCT thorax shows narrowing of the oesophageal lumen

DISCUSSION :

Small cell carcinomas (SCCs) are more often described in lungs, but rarely laryngeal, pancreatic, stomach, prostatic, uterine, sweat glands, and esophageal locations are reported. Esophageal and extrapulmonary small cell Carcinoma (EPSCC) was described first by McKeown in 1952³.

Primary small cell carcinoma of the esophagus (PSCCE) is a rare, rapidly progressive, and highly metastatic disease with poor prognosis if untreated. The incidence of PSCCE between all esophageal malignancies is from 0.05 to 2.4% in western populations, and this rate rises up to 7.6% in Chinese and Japanese literature^{4,5,6}. For instance, its incidence has been reported as 3/100,000 in Europe and USA, while it is 165–200/100,000 in Eastern Turkey, Northern Iran, and China. This tumour is mostly reported in men with a male-to-female ratio reported as 2:1. It has often been reported between the fourth and the seventh decades.

Major symptoms are progressive dysphagia, retrosternal pain, and rapid weight loss. In some cases, hoarseness and upper gastrointestinal tract bleeding have been reported as the primary symptoms. Rarely, severe cough is the primary and leading symptom. Lesions are usually confined to middle and lower esophagus. Hematogenous metastases of PSCCE are mainly extended to liver, lung, and bones^{4,5,6,7}.

Endoscopic and radiological findings of PSCCE resemble squamous or adenocarcinoma of the esophagus. Definitive diagnosis of PSCCE is diagnosed by cytological examination with esophageal abrasive balloon and endoscopic punch biopsy. There are two view points on the histological origin of PSCCE. The first is that PSCCE originates from neuroendocrine cells of the submucosal gland or stratum basal, that is, the major precursor uptake and decarboxylation cells, as histologically confirmed. The second is that PSCCE originates from multipotential stem cells of the endoderm. Most of these cells may be differentiated into squamous cell carcinoma, and some are differentiated into adenocarcinoma or small cell carcinoma. This is due to the diversity of morphological, immunohistological, and electron microscopic features of PSCCE, in addition to the coexistence of PSCCE with squamous cell carcinoma and / or adenocarcinoma⁶.

Approximately 5% of all the small cell carcinomas are extrapulmonary. Extrapulmonary small cell carcinoma (EPSCC) is called as limited disease (LD) and extensive disease (ED) as in pulmonary SCC. LD was defined as a localized tumour with or without regional lymphnode involvement. The cases with distant organ or lymphnode invasion referred to ED. The standard of treatment for PSCCE has not been established yet due to the paucity of cases. Treatments such as operation alone, local

radiotherapy, chemotherapy alone or operation with adjuvant therapy have been reported. In the limited disease, after surgical resection, short-term results of chemotherapy and radiotherapy are good, although long-term results are still poor. In a series of 29 patients with limited disease treated with only surgery, average survival was 8 months.⁸ Also in a series of 20 patients with limited disease patients treated only with radiotherapy, average survival was 5 months.⁹ After the basis of biological behavior, chemosensitivity, radiosensitivity, and some satisfaction in the treatment of small cell lung carcinomas, systemic chemotherapeutic agents PSCCE came to the fore. In early detected cases, surgical resection combined with radiotherapy and chemotherapy is the best way to treat PSCCE. In advanced stages, multiagent chemotherapy is the treatment of choice, and radiotherapy can be used for palliation. PSCCE is an extremely rare, rapidly progressive, and highly malignant characterised esophageal pathology and prone to early metastasis. In these cases, treatment must be quickly decided and started as soon as possible. The treatment is multimodal. Surgery is the standard treatment in limited stages. In advanced stages, radiotherapy with multiagent chemotherapy is a treatment choice. Despite all treatment principals, prognosis is still poor in these cases. Treatment protocols in EPSCC are similar to those in lungs and can be treated with cisplatin based regimens for chemotherapy. Surgery is of benefit in LD. Multimodal therapy including chemotherapy and radiotherapy should be preferred in EPSCC even if the diagnosis was established in the early period. In 34 EPSCC cases studied by KO Kim et al., 23 of the cases had LD and 11 had ED, and 6 (17,6%) of these were reported as esophageal origin 6 (17,6%) and as thymus origin 6 (17,6%). Overall survival was found as 19.8 months in LD and 7 months in ED. Overall survival was estimated as 14 months for all the cases. Multimodal therapy principles were applied depending on the patient's suitability both in LD and ED cases. The most commonly used chemotherapy regimen was the combination of etoposide and platinum compounds (cisplatin or carboplatin).¹⁰ Extrapulmonary-intrathoracic SCC (esophageal, thymus, etc.) and pulmonary SCC are rapidly progressive malignancies.¹⁰ Similarly to pulmonary small cell carcinoma, oesophageal small cell carcinoma remains to be a challenge for medical therapy.

CONCLUSION :

Oesophageal scc is relatively rare, rapidly progressive malignancy with poor prognosis. Due to paucity of case report in our country (especially in north east) we urge all the researchers to come forward with such a rare case to publish in various scientific research journals which will help us to understand the prevalence of the disease in our country and the various clinical findings and response to available different modalities of treatment.

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Cryptococcal Meningitis in Immunocompetent Patient

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Abstract

The incidence of cryptococcal meningitis is increasing due to increase in prevalence of human immunodeficiency virus (HIV) infection. Cryptococcal meningitis is a rare infection in immunocompetent patients. Early diagnosis and initiation of appropriate antifungal therapy can reduce mortality as the disease manifestations can be severe. In this case report, a 33 yr old immunocompetent male presented to SMCH with fever, headache, vomiting and photophobia and subsequently was diagnosed to be a case of cryptococcal meningitis. He was given specific antifungal medication.

Key words: Cryptococcal meningitis, immunocompetent patient, *Cryptococcus neoformans var. neoformans*, *Cryptococcus neoformans var. gatti*, CD4+ T cell.

INTRODUCTION :

Cryptococcal Meningitis is a serious subacute or chronic central nervous system infection caused by encapsulated yeast like fungus, *Cryptococcus neoformans*.¹ Cryptococcus is by far the most common cause of fungal meningitis. Cryptococcosis is a systemic infection caused by the encapsulated yeast fungus, *C. neoformans*.² Infection is acquired by inhalation of the organism and could be asymptomatic and limited to the lungs, especially in the immunocompetent host.³ Haematogenous dissemination, especially to the meninges, and fatal outcome occurs in patients with other disorders, particularly malignancy, diabetes mellitus, treatment with corticosteroids and infection with human immunodeficiency virus.⁴

The most important clinical manifestation is chronic meningitis.⁵ Cryptococcal meningitis presents as a subacute meningoencephalitis.⁶ Meningitis is the most common neurological presentation, though multiple small cryptococcomas or a single large granulomatous lesion and abscess may also occur, presenting with symptoms of a mass lesion, seizures, or focal neurological deficits.²

A Study from Australia showed that the two most common strains of *Cryptococcus* had different epidemiological features. *C. neoformans var. neoformans* primarily caused meningitis in immunosuppressed patients, whereas *C. neoformans var. gatti* infected healthy hosts.² *Cryptococcus neoformans* is a saprophytic encapsulated yeast with a worldwide distribution in soil contaminated with avian excreta, mostly from pigeons.⁷ The first environmental isolation of *C. gattii* (serotype B) was reported by Ellis and Pfeiffer from Eucalyptus trees in 1990.⁸

In Australia and New Zealand, up to 20% of all *C. neoformans* cryptococcosis has been reported to occur in immunocompetent individuals.⁹ A study was conducted in Bellary, South India and the overall prevalence of cryptococcal meningitis was found to be 8.3% and the prevalence of cryptococcal meningitis among the immunocompromised patients was found to be 16.6%.¹⁰

CASE REPORT :

A 33 yrs old male from Karimganj district, Assam presented with headache for 3 months duration which was dull in nature, diffuse and increased progressively. There was associated vomiting, photophobia, blurred vision and intermittent diplopia. Patient also gave history of fever for 3 months which was low grade, intermittent. He was complaining of weight loss, loss of appetite and giddiness. He was prescribed antitubercular drugs from some hospital

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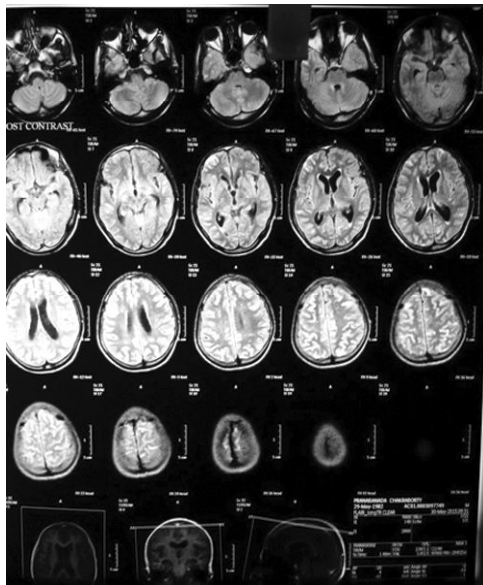


Fig: Postcontrast T1 flair image showing meningeal enhancement

but he did not respond to therapy. He was admitted in Silchar Medical College where investigations were done. Patient was conscious oriented, higher mental functions were normal and neck rigidity was present. His BP was 120/80mm of Hg, PR 80/min, cervical lymphadenopathy was present on left side. Fundoscopy revealed papilloedema.

His investigation reports showed TC 7350/ μ L, differential count normal, Hb 12.7 g/d L, ESR 5 mm AEFH, PLT 256000/ μ L, RBS 102mg/d L, S creatinine 1mg/ d L, S sodium was 134.4mmol/lit, S potassium 4.34mmol/lit. LFT, URE were normal. Stool RE, USG abdomen, Chest X ray, ECG were normal. HIV I and II were non reactive. CSF study was done and it revealed protein 78mg/d L, glucose 51.3mg/d L, cell count 120/ μ L, mononuclear cells 86% and polymorph was 14%. CSF opening pressure was high. CSF Gram staining showed few pus cells and gram positive Cryptococcus and fungal stain showed Cryptococcus. CSF was negative for MTB complex, HSV 1 and 2. CSF and serum for cryptococcal antigen were positive. MRI brain with contrast showed diffuse leptomeningeal enhancement over cerebral hemisphere, brainstem and cerebellum. Patients CD4+ T cell count was 655/ μ L.

Patient's immunoglobulin electrophoresis was done and showed total IGA 3.3g/L, IGG 13.70g/L, IGM 1 g/L. Patient was given inj Amphotericin B and Flucytosine for 2 weeks followed by oral fluconazole 400mg/day for

10 weeks. After receiving antifungal treatment patient got improved without residual neurological deficit.

DISCUSSION :

Cryptococcosis is an important opportunistic fungal infection causing an estimated 1 million cases and 625,000 deaths per year due to central nervous system disease among patients with human immunodeficiency virus worldwide.¹¹ Although cryptococcosis is most often associated with HIV infection, in many centers, especially in more developed countries, the majority of cases occur among non-HIV-infected individuals including transplant recipients; patients who are receiving immunosuppressive agents such as glucocorticosteroids, cytotoxic chemotherapy and patients with underlying disorders such as organ failure syndromes, innate immunologic problems, common variable immunodeficiency, and haematologic disorders.¹²

Cryptococcal meningitis is rare in immunocompetent patients. *C. gattii* has recently been responsible for an ongoing outbreak of cryptococcosis in apparently immunocompetent humans and animals on Vancouver Island and surrounding areas within Canada and the northwest United States.¹³ In this article, it has been shown that cryptococcal meningitis can occur in immunocompetent individual and if patient is diagnosed early and given specific antifungal treatment, clinical outcome is good.

CONCLUSION :

Cryptococcal meningitis though being a fatal HIV related opportunistic infection can rarely affect immunocompetent patients too. This highlights the importance and necessity of suspicion followed by proper and timely management of cryptococcal meningitis in non resolving subacute meningoencephalitis cases.

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Ventricular Tachycardia an initial Presentation in sarcoidosis

D J Dutta*, M Debbarma**, S Kakati***, A Dutta****

Abstract

Sarcoidosis, a systemic granulomatous disease of unknown etiology involves the heart in less than 5% of cases. Though clinically apparent cardiac sarcoidosis is an uncommon entity, a life threatening ventricular tachyarrhythmias (VT) may be the first presenting symptom and rarely a high degree heart block requiring an early intervention. We report a case of cardiac sarcoidosis for the first time from North-East India presenting with complex arrhythmia.

KEYWORDS : *Systemic granulomatous disease, Ventricular tachycardia, cardiac sarcoidosis, complex arrhythmia*

INTRODUCTION :

Sarcoidosis is a systemic granulomatous disease of unknown etiology involving many organs like skin, eyes, lung, lymph nodes, liver, spleen.¹ Although only 5% of cases involve the heart, patients may present with acute cardiac failure, arrhythmias or sudden death.¹ Cardiac sarcoidosis has three histologic phases: edema, granulomatous infiltration, and fibrosis and eventual scarring.² Usually involvement is predominantly myocardial affecting the left ventricular free wall, basal septum, right ventricle, and finally the atrial wall. This predisposition is believed to be due to increased myocardial mass in these areas. Standard diagnostic criteria for cardiac sarcoidosis developed by the Japanese Ministry of Health and Welfare lack sensitivity and specificity in the absence of diagnostic myocardial biopsy.^{3,4} Even though the gold standard of diagnosis is myocardial biopsy, it has limited utility due to its invasive nature and high false-negative rate secondary to patchy cardiac infiltration.⁵ In its early stages, cardiac sarcoidosis is usually clinically silent, rapidly progressing to heart failure, arrhythmias, and even sudden cardiac death. Currently,

there are no established guidelines for early diagnostic approach. However, in a recent review article by Mantiniet al.⁶, a step-wise algorithm for patients with suspected cardiac sarcoidosis was proposed. According to the algorithm, patients with proven extra-cardiac sarcoid or patients with suspected sarcoid should be screened with detailed history, physical examination, ECG, and chest X-ray. If the patient is symptomatic, the ECG is abnormal (VT, Mobitz type II or complete heart block on 12-lead, [100 PVCs on 24-hour Holter monitor, or T-wave alternans) or X-ray demonstrates cardiomegaly, follow-up testing is recommended. In a patient with extra-cardiac sarcoid, with no Coronary artery disease (CAD) by angiography, further imaging with CMRI, 18F-FDG-PET, rest/stress technetium-99m (99mTc) sestamibi, or 201-thallium (TI) plus 67-gallium is recommended.⁶

CASE REPORT :

A 28 years old man who is a policeman by occupation presented with acute onset palpitation along with vomiting for five episodes after heavy exercise. There was also history of abdominal fullness and abdominal pain radiating to the back. There was also history of dizziness and syncopal attack. He was treated in the local hospital and later on referred to this institute after 24 hours.

At the time of presentation to the institute the patient complained of shortness of breath and dizziness. He is a non-smoker, non-diabetic and non-hypertensive, there is no history of chest pain, paroxysmal nocturnal dyspnea,

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and orthopnea and no family history of premature CAD or stroke. The patient did not give any history of respiratory illness or any other serious illness in the past.

On physical examination, the patient was restless and disoriented. The vital signs were temperature 97.8 F, blood pressure 84/50 mmHg, heart rate was 168, beats/min, regular; respiratory rate 28 breaths/minute, and oxygen saturation 86% on room air. The abdomen was soft, nontender, nondistended, with no hepatosplenomegaly. There was no clubbing, cyanosis, or edema. No skin lesions were noted. The patient was transferred from emergency department to the cardiac ICU and ECG showed the following (Monomorphic VT)

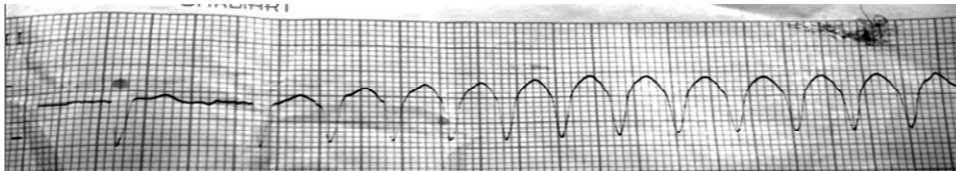


Figure 1. ECG of the patient showing Monomorphic Ventricular Tachycardia

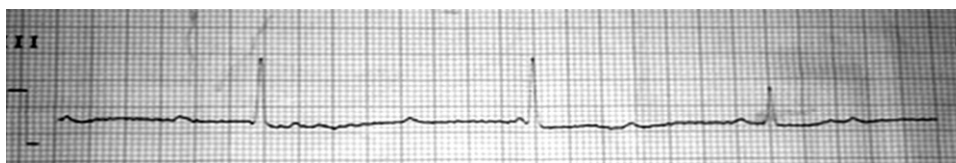


Figure 2. ECG of the same patient showing complete atrio-ventricular dissociation

A synchronized electrical cardioversion successfully terminated his VT and patient was started with amiodarone 150 mg IV infusion. The patient suddenly developed complete AV dissociation and was managed with a temporary pacemaker implantation and subsequently patient has been managed with permanent pacemaker. After stabilization of the patient echocardiography showed moderate dilation of the left ventricle (LV), with overall



Figure 3. CXR showing Cardiomegaly

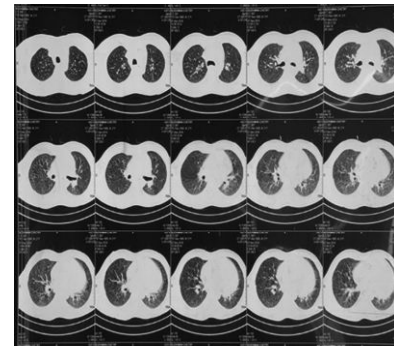


Figure 4. CT thorax showing para-hilar lymphadenopathy

mild-moderate reduction of LV systolic function with an ejection fraction (EF) of 49%. The routine investigations showed Hb-14.2 gm/dl, ESR= 05 mm AEFH, TC- 7,800 and DLC- N 74 L 18 E 06 M 02 B 00, KFT was within normal limits, S.Na-129.2 mmol/L, K- 4.94 mmol/L, Ca -7.8 mg/dl, RBS= 103 mg/dl, S. Amylase and Lipase were within normal limits.

Cardiomegaly was noted on CXR and HRCT thorax revealed cardiomegaly with multiple subcentimetric lymph nodes in the subcarinal, prevascular and aorto-

pulmonary regions with largest node measuring 9.3 mm in short axis diameter, great vessels of thorax appear normal. Serum ACE level was 83 U/L (normal- 8.00 TO 65)

DISCUSSION :

Cardiac sarcoidosis in systemic sarcoidosis is one of the least common manifestations. In a recent review, the incidence of clinical heart involvement was reported as approximately 5%, whereas at autopsy the incidence was considerably higher (20 to 25%).⁷ The course of sarcoidosis can be indolent; however, acute complications in cardiac sarcoidosis can lead to sudden cardiac death.⁸ Non-caseating granulomas serve as foci for abnormal automaticity and cause changes in the ventricular activation and recovery process, which explains the re-entry mechanism that is thought to lead to VT in cardiac sarcoidosis. Although possible cases of cardiac sarcoidosis should initially have an echocardiogram to look for supportive findings such as regional wall motion abnormalities, thickening of IVS with bright shadow consistent with infiltration and impaired left ventricular EF,

these findings are not specific. Cardiac MRI with gadolinium enhancement and PET scanning are valuable aids in the diagnosis of myocardial sarcoidosis and are considered superior to gallium-labeled or technetium labeled nuclear scans.⁹ Reports suggest that the sensitivity of detecting sarcoid granuloma on endomyocardial biopsy is around 20%; hence a negative biopsy does not exclude the disease.¹⁰

Sarcoidosis that involves the heart warrants prompt treatment with corticosteroids with or without other immunosuppressive agents. A recent study showed that corticosteroids are more helpful in patients with mild to moderate left ventricular function impairment (left ventricular EF of 30 to 50%), whereas those with a severely reduced left ventricular EF of less than 30% in the late stage of disease did not benefit (probably because of irreversible myocardial damage and fibrosis).¹¹ The patient in our case presented in the early stages and have shown response to steroids. Ventricular arrhythmias are common in cardiac sarcoidosis but are often refractory to antiarrhythmic drugs including amiodarone. Most authorities recommend placement of an electronic pacemaker for complete heart block and an automatic implantable cardioverter defibrillator (AICD) for ventricular fibrillation or tachycardia and markedly reduced left ventricular ejection fraction.¹² Cardiac transplantation is a useful option in cardiac sarcoidosis refractory to medical management, however, some studies have shown a trend towards increased mortality. However, with progress in prevention and treatment of ventricular arrhythmias, the primary cause of death in cardiac sarcoidosis has changed from sudden death to congestive heart failure.

In our case on follow up the patient had decrease in Serum ACE level after corticosteroid therapy and improvement in LV ejection fraction and is presently on oral Amiodarone 200mg once daily.

CONCLUSION :

Cardiac presentation in Sarcoidosis is usually subclinical however it may sometime present with life

threatening conditions like ventricular tachycardia and high degree heart block. Thus a patient presenting with complex arrhythmia in young age should be thoroughly investigated for cardiac sarcoidosis. A strong clinical suspicion can be supported by advanced cardiac imaging to support the diagnosis. Steroid therapy is beneficial when used relatively early in the course of the disease and a strong consideration for prophylactic implantation of an AICD should be considered, particularly in the presence of ventricular arrhythmias or reduced ejection fraction.

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