ORIGINAL ARTICLE

CLINIC0-PATHOLOGICAL FEATURES OF LUNG CANCER AND INCIDENCE OF FAMILIAL MALIGNANCIES IN A STUDY POPULATION IN KARACHI

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ABSTRACT:

A prospective, non randomized multi-institutional study was conducted to assess the clinico-pathological features and incidence of familial lung cancer in patients presenting in major oncology centres in Karachi. A total of 71 patients were interviewed all but 4 were married. Majority belong to middle and low income group. More than half did not have University education. More than two third were urban dwellers. About half had white collared jobs. Tobacco use was rampant in the study population. Majority had good ECOG performance status at presentation. More then 50% had diabetes and hypertension and comorbids. Chest pain, cough, weight loss and breathlessness were the chief presenting complaints, while consolidation/collapse, effusion and lymph adenopathy were major physical findings. Half of the study population underwent bronchoscopy biopsy as diagnostic procedure. Three fourth of them had NSCLC. Squamous cell carcinoma was the major histological type. Among NSCLC early and advanced staged disease was evenly distributed while extensive disease was predominant stage of SCLC. Family size, particularly the extended family, in our population appears to be fairly large. No direct association between family history and lung cancer was statistically determined.

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INTRODUCTION:

Lung cancer is among the most commonly occurring malignancies in the world and is one of the few that continues to show an increasing incidence. In the United States, lung cancer is the leading cause of cancer death in men, and it surpassed breast cancer as the leading cause of cancer death in women in the latter part of 1980's[1]. In the year 2003, there was approximately 1, 71,900 new cases and approximately 1, 55,000 deaths from this disease.

Excluding this malignancy, most developed countries have shown declines in death rates from cancer in the last 20 years. During the same period in countries such as the United States and Canada, the death rate from lung cancer increased more than threefold but, in the last 5 years, it has finally begun to decline. In developing countries, the death rate from lung cancer continues to accelerate. These changes appear to be effected significantly by the observed difference in smoking habits and cigarette tar levels in developed and developing countries[2].The incidence of lung cancer now exceeds 70 per 100,000 men in the United States. As we enter the twenty-first century.

It is expected that the altered smoking habits of the nation's population during the last two decades and the decreased tar content of cigarettes consumed in the United States will lead to a further decline in lung cancer incidence.

Mortality

In the United States, only 14% of patients who develop lung cancer survive 5 years. These mortality rates (>150,000/ year) far exceed those of the acquired immunodeficiency syndrome epidemic. However, this survival rate has only slightly increased in the last two decades, and it appears unlikely that marked

improvements will occur in the near future. With the anticipated decreased incidence, however, it is hoped that the lung cancer epidemic, at least in developed countries, will abate and that the total number of deaths per year attributed to this cancer will decline even further.

Evidence for a genetic predisposition

There is limited evidence that genetic factors may contribute to lung cancer risk. Variations in the metabolism of carcinogens have been implicated [3]. The pathways to create these toxic metabolites are genetically determined. The metabolism of the antihypertensive drug Debrisoquin is genetically determined by a single gene. The metabolisms of many drugs and chemicals correlate with that of debriosquin[61], and this may also apply to carcinogenic components o cigarettes smoke. Although this has not been proven for any one substance with respect to lung carcinogenesis [3-9]. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition [9-11]. Braun et al[8] conducted a twin cohort study and found no genetic factors to be predictive of lung cancer. Highway et al[11] observed that the allele K-ras occurred in 29% of non-small cell lung cancer (NSCLC) cases, compared with 15% of controls (P=.03). Numerous other chromosomal abnormalities (Rearrangements and deletions) are present in lung cancer. These abnormalities are thought to result from the effects of carcinogens or the genetic instability observed in malignant transformation.

Although the molecular and genetic events underlying the pathogenesis of lung cancer are an area of active investigation, no genetic abnormality has conclusively defined the risk of lung cancer. In NSCLC the most frequently identified abnormalities are deregulation of tumor suppressor gene , aberrant expression of the epidermal growth factor receptor (EGFR) and one of its ligands, and the presence of K-ras abnormalities in adenocarcinoma (discussed in new potential prognostic Markers) [12-13].

AIMS & OBJECTIVES

- To asses the clinico-pathological features of lung cancer.
- To determine the familial association in 1st and 2nd degree relatives of patients presenting with lung cancer

STUDY DESIGN

- Prospective; Non-randomized and multi institutional
- All patients presenting with histological confirmed cancer between November 1998 to February 1999 were interviewed and their medical record reviewed familial cancer Performa were filled. None of the patient was excluded. Data was analyzed on EPI-info package.

PATIENTS AND METHODS:

The study was conducted from October 1998 to March 1999. Patients with histologically proven lung cancer were interviewed and study Performa was completed. The study institutions were Ziauddin Cancer Hospital, Baqai Institute of Oncology, Liaquat National Hospital and JPMC. A separate for Performa with reference to family history and incidence of cancer was also filled. First degree relatives were defined as father, mother, sons, daughters, brothers and sisters. Second degree relatives were defined as maternal grand parents, paternal grand parents, grand sons, grand daughters, maternal aunts, maternal uncles, paternal aunts and paternal uncles. Third degree relatives were excluded from the study. The resultant raw data was fed into computer and analyze on EPI package.

Table: 1 DEMOGRAPHICS OF PATIENTS	NUMBER	PERCENTAGE
Number of patients	71	
Mean age in year (± SD)	58.9 ± 10.2	
Marital status :		
Single	4	5.6
Married	67	94.4
Socio-economic status :		
High	3	4.2
Middle	27	38.0
Low	40	56.3
Unknown	1	1.4
Educational status :		
Illiterate	16	22.5
High school	22	31.0
College	14	19.7
University	19	26.8
Predominant Habitat :		
Urban	56	81.7
Rural	13	18.3
Occupation :		
Office Based	36	50.7
Field works	24	33.8
Factory based	6	8.5
Unknown	5	7.0

Table: 2 Tobacco use:	NUMBER	PERCENTAGE
Cigarette smoking	63	88.7
Packs / day		
½ Packs	5	8.3
½ - 1 packs	21	35.0
1-2 Packs	31	51.7
> 2 Packs	3	5.0
If quit smoking, have Long?		
< 5 years	18	94.7
> 15 years	1	5.3
USE OF TOBACCO IN OTHER FORMS		
Tobacco with pan	25	56.8
Naswar	9	20.7
Bidi	2	4.5
Tobacco leaves	1	2.3
Chalia with Tobacco	4	9.1
Qiwam	3	6.8
Alcohol use	4	5.6

Table: 3 CHIEF COMPLAINTS	Number	Percentage %
Chest pain	60	84.5
Cough	57	80.3
Weight loss	49	69.0
SOB	48	67.6
Fever	42	59.2
Sputum production	26	36.6
Hemoptysis	22	31.0
Limb Weakness	13	18.3
Facial swelling	11	15.5
Disorientation	8	11.3
stammering speech	8	11.3

Facial palsy	2	2.8
Visual disturbances	2	2.8

Table: 4 PHYSICAL FINDINGS Number percentage %

Consolidation	30	50.7
Collapse	20	28.2
Effusion	19	26.8
Lymphadenopathy	17	23.9
Edema	12	16.9
Hepatomegaly	10	14.1
SVC obstruction	8	11.3
Jaundice	7	9.9
Clubbing	6	8.5
Pallor	5	7.0
Horner's syndrome	3	4.2
Cyanosis	2	2.8
SIADH	2	2.8

Table: 5 DIAGNOSTIC PROCEDURES Number percentage %

Bronchoscopic biopsy	37	48.1
Lymph node biopsy	19	24.6
CT guided biopsy	10	13.0
U/S guided biopsy (liver mets)	7	9.1
Pleural Biopsy	4	5.2
Type of malignancy		
NSCLS	53	75.7
SCLC	18	24.3

Table: 6 HISTOLOGY Number percentage %

NSCLC		
Squamous cell carcinoma	30	42.3
Adenocarcinoma	19	26.8
Undifferentiated large cell Carcinoma	4	5.6
SCLC		
Oat cell	13	18.3
Undifferentiated	3	4.2
Intermediate cell	1	1.4
Mixed cell	1	1.4
Nuclear grade :		
Well differentiated	18	25.4
Moderately differentiated	22	31.0
Poorly differentiated	19	26.7
Unknown	8	11.3
Undifferentiated	4	5.6

Table: 7 STAGING AND MANAGEMENT	Number	percentage %
TNM Stage of NSCLC		
I	12	16.9
II	12	16.9
III	15	21.2
IV	14	19.7
Staging of SCLC	3	4.2
Limited disease	12	16.9
Extensive disease	3	4.2
Radiotherapy		
Therapeutic	17	58.6
Palliative	12	41.1
Setting of chemotherapy		
Neo-adjuvant	10	62.5
Adjuvant	4	25.0
2nd Line	2	12.5

Table: 8 FAMILIAL PREDISPOSITION	Number	percentage %
Family history and cancer	2	2.8
Total # of 1st degree relations	834	
Mean # of 1st degree relations perfectly	12.3±5.6	
Type of cancer	TCC Bladder 1	
Total # of 2nd degree relations	2605	
Mean # of 2nd degree relations / Family	36.7±23.6	
Type of Cancer Head & Neck	1	
CONSANGINUOUS MARRIAGES	30	42.3

Results

A total of 71 patients were enrolled in the study. All but 4 of them were married and head families majority belong to low socio economic group (Monthly income Less than Rs. 3000/= per month) (56.3%) only 3 could be classified as belonging to high income group majority were either matriculates or illiterate only 19 among the study population had university or equivalent education. Significant majority (81%) belong to urban habitat. This could be attributed to low level education, poverty and lack of basic health care facilities in the rural areas. Almost 50% of the study population white-collared jobs working in offices, while rest were in fields and factories. Significant number of patients (88.7%) were smokers and almost (50%) smoked two packs a day about (95%) left smoking after the diagnosis of cancer. Tobacco usage in non smoking form was also common among the study population 44 patients had history of using pan with Tobacco, Niswar or Qiwam etc. a significant majority (56.8%) used pan with tobacco. Interestingly, there were no cigar or pipe smokers in the group. This could be attributed to the trend of pipe and cigar smoking among the high socio-economic group. Quiet a few patients presented with additional diagnosis of hypertension, diabetes and cardiovascular diseases. This could again be attributed to their habit of tobacco usage along with their co-morbids. More than half of the study population had good performance status and they were fully active or they were able to carry out day to day work independently. Major presenting complaints were chest pain, cough, shortness of breath and weight loss. A few had neurological symptoms like disorientation, limb weakness, facial palsy and visual disturbances. Among physical findings, consolidation- collapse was the commonest. A few also presented with SVC obstruction and SIADH. About half of the study population, underwent bronchoscopic biopsy as diagnostic procedure while lymph node biopsy was the 2nd commonest procedure. A few underwent pleural biopsy and ultrasound guided liver biopsy for metastatic disease. 3 fourth of the study population had NSCLC. Squamous cell carcinoma was the predominant histological sub-type (42.3%) Bulk of the patients had moderately or poorly differentiated tumor grade. As expected majority presented with advanced disease (stage III- IV NSCLC/extensive disease SCLC). Detailed family history revealed a trend towards having large families when compared to western

populations. Mean number of first degree relatives among the study population was around twelve while the mean number of second degree relatives was around 37, which signifies a trend towards having a larger extended family. Only one person among the first degree relatives was found to have transitional cell carcinoma of urinary bladder. While only one had carcinoma of tongue among the second degree relatives. In our society there seems to be a significant trend towards having marriages within the family as shown in the data (42.3%).

Discussion:

It has been thought for some time that squamous cell cancers have the best survival. In some series of early-stage resectable lung cancer, this appears to be true, but it is less clear in more advanced stages, for which cooperative group studies show little or no differences between the various non-small cell histologies. A consensus meeting sponsored by the International Association for the Study of Lung Cancer in Paris in June 1992 concluded that because of differences in criteria, decisions on histologic subtypes by different pathologists, and other factors, one should not assume that any of the histologic subtypes of NSCLC have a superior survival to any other of similar stage. The all-inclusive term NSCLC has more clinical and prognostic relevance. SCLC generally has the worst overall survival because of its frequent and more rapid spread to the mediastinum and major organs. With improvements in treatment, this may change over the in coming years. Patients with the best prognosis may often by asymptomatic; an abnormality may be found on routine physical examination or routine chest radiograph before a surgical procedure. Most patients, however, are symptomatic and present with more advanced disease, which may account for the generally poor survival of patients with lung cancer (13 percent 5-year survival)[14]. The clinical features can be arbitrarily divided into those due to local problems in the lung, those due to local/regional spread, and finally those due to widespread metastases. This is very simple but practical approach to thinking about this disease since the symptoms fit so well into these anatomic categories. The local/regional symptoms arise primarily from involvement of the mediastinum and associated structures. Superior sulcus tumors may lead to the classic symptom complex of Pancoast syndrome when they extend to the brachial plexus, which results in anatomically appropriate symptoms including pain and sensorimotor signs. If the sympathetic trunk is involved, a classic Horner syndrome may occur. The patient with superior vena cava syndrome, resulting from mediastinal involvement, often presents initially with periorbital and facial edema, particularly early in the morning after having been in a horizontal position for a number of hours. This may disappear by midmorning or later in the day. Patients may also complain of headache associated with cerebral edema and, once compensation for the venous obstruction with new vessel formation on their anterior chest wall may be noticed by the patient. As previously mentioned, an important, relatively uncommon, but distinct subtype of adenocarcinoma is bronchoalveolar carcinoma[15]. it can be unilateral or bilateral and often causes an infiltrate similar to that seen in pneumonia. Classically, patients with bronchoalveolar carcinoma produce copious amount of mucoid sputum at the end stage of their disease, frequently developing severe dyspnea along with frothy sputum; they can literally down in their own secretions in the final stages. Systemic manifestations are common to all advanced tumors and are not necessarily specific for lung cancer. Weight loss, associated with poor prognosis, and cachexia are frequent, the former even being present in totally resectable cancer. Spread to the other lung adrenal glands, bone, liver, and brain will result in manifestations appropriate to the site of involvement. However, non of these is specific for lung cancer. Paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone secretion or ectopic corticotropic hormone production with cushing syndrome are seen most commonly in patients with SCLC. Less common are the syndromes of cerebellar ataxia, dementia, and sensorimotor neuropathies. Neurologic symptoms are usually secondary to metastatic tumor in the brain or spinal cord, but occasionally may be paraneoplastic. The Eaton Lambert syndrome is seen rarely in patients with SCLC who have nonspecific weakness. It is characterized mainly by muscle weakness and fatigue, especially in the pelvic girdle and thigh, along with other less specific complaints. Patients may have difficulty climbing stairs and getting out of a chair. Muscle strength improves with exercise, in contradistinction to myasthenia gravis.

In two studies of note from Pakistan by Fauzia Rana et al [16] from Lahore and Z. I Hussain[17] from Multan conducted survey on similar lines. However, their aims and objectives were not directed towards looking into familial trends. In both the studies, Clinico-Pathological features were similar to what we have concluded except that in Fauzia Rana's study [16] 25% of the subjects were non smokers.

Inherited predisposition to lung cancer appears to be a complex genetic trait. In experimental models murine indred strains with high genetic predisposition to lung cancer are available, as well as resistant strains. A major locus affecting inherited predisposition to lung cancer in mice has been mapped on chromosome 6 near the K-ras gene[18].Additional "minor" loci have also been mapped; dominant lung

tumor resistant loci have also been demonstrated in the mouse genome[18]. In human, the specific familial genetic changes predisposing to lung cancer are largely unknown, although there are many observations suggesting that they play crucial role in development of significant proportion of malignancies[18]. In human, the tobacco smoking represents the main risk factor for lung tumors, however familial clustering has been reported also in non-smoking patients[18]. Lung cancer in a first-degree relative is associated with around 7-fold increased risk of lung cancer among smokers in the 40-59-year-old age group[18]. Offspring of non-smoking cases comprises another lung cancer high risk group. Among at-moderate-risks smokers the estimated risk at the same age group are essentially the same as in the high risk non-smokers. Among non-smoking high risk individuals the estimated risks at ages 40, 60 and 80 years are around 15, 75 and 90% respectively. A positive family history does not increase lung cancer risk among non-smokers 60-84 years of age or their relatives[18]. Pedigree and clinical criteria analogous to those described by ICG-HNPCC for colorectal cancer and characteristics of mendelian dominant inheritance pattern can be matched only exceptionally among series of consecutive lung cancer cases[18]. Laboratory data supporting epidemiological observations on the occurrence of hereditary lung cancers include such findings as: higher rate of microsatellie instability tumors from patients with familial clustering of micro satellite association of constitutional chromosome 9 aberrations with familial aggregation of lung tumors and probably increased lung cancer risk in individuals with particular alleles of inherited genes or phenotypes for drug metabolizing enzymes[18].

Although we were not able to find in a familial association with lung cancer, a recent study from Detroit, USA[19] established a link between family history and lung cancer. Incidence of familial lung cancer in African-Americans was more common than Caucasians. Rest of the clinico-Pathological features were similar to our study.

Conclusions :

There does not seem to be a significant difference between in clinico-pathological features in the study population when compared to data from elsewhere[20]. There was no direct evidence of incidence of familial lung cancer among the study population. The two patients found among the relatives of the patients in the study population can be attributed to their tobacco usage rather than any genetic predisposition. As the sample size of the study was small, there is a need to conduct larger population based studies to obtain more meaningful data.

Declaration :

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