

A PATTERN OF CARCINOMA OF LUNG AS SEEN IN A TERTIARY CARE HOSPITAL

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ABSTRACT

*This cross sectional descriptive study was conducted to assess clinicopathological characteristics of lung cancer in 142 patients, 116 males and 26 females, from various regions of Punjab presenting with clinical features consistent with the diagnosis of lung carcinoma. They were admitted to Gulab Devi Chest Hospital (GDCH), Lahore, Pakistan from January 2005 to January 2007. Our observations revealed that the most prevalent malignancy among these patients was non small cell lung carcinoma including squamous cell carcinoma and adenocarcinoma in males and females respectively. Most common affected age groups were between 41-60 years (n=82) and 51-70 years (n=15) in males and females respectively. Squamous cell carcinoma followed by small cell lung carcinoma were commonly associated with smoking in both genders. Immunohistochemistry was employed for the confirmation of diagnoses in some (n=35) cases. We observed that 4 of 10 (40%) large cell lung carcinomas were strongly positive with HDC. The remaining 06 (60%) large cell lung carcinomas though negative for HDC, were strongly positive with Cyfra 21-1. All small cell lung carcinomas, atypical and typical carcinoids were also strongly reactive to HDC immunostaining. Antimucin antibody was also strongly positive and negative in each 02 of the 04 (50%) poorly differentiated adenocarcinomas where all of them were strongly reactive to Cyfra 21-1. It is **concluded** that lung cancer is more common in males and is strongly associated with smoking. Hence, interventional measures for prevention and early but correct diagnosis of bronchogenic carcinoma is needed. The role of tumour markers can be very useful in finalizing cases which are difficult to be differentiated.*

INTRODUCTION

Cancer of lung is the most common organ malignancy and is one of the most prevalent cause of cancer-related deaths worldwide^{1,2}, with approximately 1.2 million deaths occurring annually^{3,4}. According to a published report by WHO report in 2005, lung cancer was the most common malignancy (age standardised incidence being 20 per 100,000) and the leading cause of cancer deaths among Pakistani men with the annual incidence and mortality rate being 42/100,000 and 19/1000 in male population that was highest among all cancers occurring in Pakistan⁵. A ten years report published by Shaukat Khannum Memorial Cancer Research Hospital, Lahore, extending from December 1994 to December 2004 in which a total of 24,758 neoplasms were seen in the registered population in the hospital comprising males, females and children. A total of 12,346 tumours were seen among males (49.9%) and 12,412 (50.1%) in females. The lung cancer comprised 1,004 cases (4.17%). Among adults (age > 18 years, both sexes combined) lung cancer was the fifth most common malignancy (n=1,003; 4.73%) and the third most common cancer among males (n=854; 7.04%)⁶.

In this study, the clinicopathological characteristics of lung cancer as reported in a tertiary

care hospital of Lahore were analysed in terms of morphological types. Male to female ratio of lung cancer in our patients, relation of the morphological type of lung cancer with male and female population, relation of lung malignancy with age and smoking history and relation of gross location of lung malignancy and cancer type. The role of immunohistochemical markers in the diagnosis of certain lung cancers is also elaborated.

MATERIALS AND METHODS

Patients:

This study was a cross sectional descriptive study comprising a total of 142 patients (116 males and 26 females) from various regions of Punjab presenting with lung cancer at Gulab Devi Chest Hospital, Lahore from January 2005 to January 2007. Relevant clinical and laboratory data of these patients were recorded in separate proformas. More than 10 years history of habitual active smoking was taken as positive history and as an important correlating parameter in both sexes.

Biopsies:

Lung biopsies of several types and of different sizes including trucut, core needle, wedge, pleural, endoscopic lung biopsy, excision biopsy, debulking

specimen, segmentectomy, lobectomy, pneumonectomy, mediastinotomy, thoracotomy and CT guided biopsies etc. were included. The tissues were processed in formalin and embedded in paraffin to form tissue blocks. From each tissue block, three sections of 3-5µm thick were cut by rotary microtome and one section was collected on frosted slides for Haematoxylin-eosin staining whereas other two on poly-L lysine coated slides.

Staining Procedures:

One section of each sample was stained with conventional H & E stain following the method of Harris's Haematoxylin. The sections were examined by two pathologists before the reports were released. Immunohistochemistry was performed using the standard Avidin biotin peroxidase method only in the tissues in which the diagnoses needed further workup and differentiation was mandatory by employing the help of a specific tumour marker. In this study, Histidine Decarboxylase (HDC) (for neuroendocrine differentiation), Cyfra 21-1 (as an epithelial marker) and Anti mucin antibodies (for mucinous differentiation of lung adenocarcinomas) were applied.

Immunohistochemistry:

A total of 35 tissue sections were subjected to immunohistochemistry because of their indefinite diagnoses or to differentiate them from other morphologically similar carcinomas or to demonstrate neuroendocrine differentiation in certain tumours. Among these, 10 were large cell lung carcinomas, 04 were poorly differentiated adenocarcinomas, 10 were small cell lung carcinomas, 06 typical carcinoids, 03 adenocarcinomas, 01 non small cell lung carcinoma and 01 sarcoma. The staining was declared positive only when three of these antibodies showed complete homogenous dark brown cytoplasmic reaction with Diaminobenzadine in at least 10% of tumour cells in case of HDC and anti-mucin antibody and >75% with Cyfra 21-1.

RESULTS

The clinical features among 142 cases of lung cancer showed that 56.3% (n=80) of 142 cases were active smokers for more than 10 years with 23% having a history of more than 25 years of smoking. Fourteen percent patients, (n=13 males and n=06 females), were on antituberculous therapy for more than two years.

As regards the sex among 142 cases, 82% (n=116) were males and 18% (n=26) were females. The age range of 116 males was from 08 years to 83 years with mean age being 46 years. A total of 64.6% (n=75) patients gave a >10 years history of smoking. The age range of 26 females presenting

at GDCH was from 12 years to 70 years with mean age being 41 years. A total of 19% (n=05) patients gave a positive history of smoking for > 10 years (Table 1).

Table 1: Presenting Clinical Features in 142 patients of lung cancer.

No.	Clinical symptoms	% age
1.	Cough and/or expectoration	(92%)
2.	Dyspnoea	(50%)
3.	Haemoptysis	(41%)
4.	Chest pain	(84%)
5.	History of smoking for > 10 years	(56.3%)
6.	Antituberculous therapy for > 2 years	(14%)

Morphological types of lung carcinoma

A diverse morphological pattern of lung carcinoma was seen. Patients presented with squamous cell carcinoma in 27 % (n=38 of 142). Among them 16% (n=6) were well differentiated, 10.5% (n=4) were moderately differentiated and 74% (n=28) were poorly differentiated. Adenocarcinoma was diagnosed in 11% (n=16 of 142). Among them 31% (n=05) were well differentiated, 13% (n=02) were moderately differentiated and 56% (n=09) were poorly differentiated. Bronchioloalveolar carcinoma formed 1.4% (n=02). Non small cell lung carcinoma was seen in 26% (n=37 of 142). Among them 57% (n=21) were well differentiated and 43% (n=16) were poorly differentiated. Large cell lung carcinoma formed 4.2% (n=06 of 142). Large cell neuroendocrine carcinoma formed 2.8% (n=04). Small cell lung carcinoma formed 18.3 % (n=26). Typical carcinoids formed 4.2% (n=06) and atypical carcinoids 2.1% (n=03). We also found one rare adenoid cystic carcinoma of lung (0.7%), one sarcoma (0.7%), one anaplastic carcinoma (0.7%) and one metastatic carcinoma (0.7%). Squamous cell carcinoma and non small cell carcinoma were the most frequent lung malignancies reported in these two years with a total number of cases being 38 (27%) & 37 (26%) respectively.

Where WD (well differentiated), MD (moderately differentiated), PD (poorly differentiated), SCC (squamous cell carcinoma), AdC (adenocarcinoma), NSCLC (non small cell lung carcinoma), LCLC (large cell lung carcinoma), TC (typical carcinoid).

It is evident that Non small cell lung carcinoma formed 31% (n =36) whereas squamous cell carcinoma formed 30% (n=34) (Table 2). These were the most commonly observed malignancies in male population. The age distribution among 116 male patients showed that 2.5% (n=03) were

between the age group of 08-20 years, 18% (n=21) in the age group 21-40 years, 51% (n=59) were in the age group 41-60 years, 26% (n=30) were in the age group 61-80 years and 2.5% (n=03) were above 80 years. Association of lung carcinoma with positive history of smoking was observed in 79.4% (n=27 of 34) patients with squamous cell carcinoma, 75% patients (n=18 of 24) with small cell lung carcinoma and 58.3% patients (n=21 of 36) presenting with non small cell lung carcinoma.

It was noticed that adenocarcinoma, 35% (n=09), was the most commonly observed malignancy in 26 female cases (Table 3). Among them, 27% (n= 07) were in the age group of 10-30 years, 15.3% (n= 04) in the age group 31-50 years and 58% (n=15) between the age group 51-70 years. Association of lung carcinoma with positive history of smoking was observed in 50% (n = 02 of 04) patients with squamous cell carcinoma, 50% (n=01 of 02) patients with small cell lung carcinoma and 01 patient with non small cell lung carcinoma.

Location wise left lung was involved most commonly i-e in 59% (n=68) male patients whereas the right lung was the most common site of malignancy in 65% (n=17) females. Right lung was involved in 38% (n=44) males and left lung was involved in 27% (n=07) females presenting with lung carcinoma. The remaining 04 cases (3%) among males and 02 cases (08%) among females were mediastinal and pleural tissues. Metastatic cancer was seen in only one male. However, upper lobe was involved most commonly on both sides with left being involved in 57% (n=39) males and 43% (n=03) females and right upper lobe was affected in 48% (n=21) males and 47% (n=08) female patients (Table 4).

Immunohistochemistry:

As regards the immunoperoxidase staining, it was performed on 37 tissue sections from various tumours where after H & E staining, we could not reach a conclusive diagnosis (Fig. 1). We observed that 40% (n=04 of 10) large cell lung carcinomas

Table 2: Morphological types of lung carcinomas in 116 male patients with different age groups and smoking history of >10 years.

Sr. No.	Morphology of lung carcinoma	Cases reported	History of smoking (%)	Age range
1.	WD SCC	06	04 (66%)	40 - 65
2.	MD SCC	03	01 (33%)	40 - 59
3.	PD SCC	25	22 (88%)	40 - 74
4.	WD-AdC	02	00	62 & 65
5.	PD-AdC	05	01 (20%)	58 - 83
6.	WD-NSCLC	21	14 (66%)	28 - 75
7.	PD-NSCLC	15	07 (56%)	35 - 82
8.	LCLC	10	03 (30%)	19 - 75
9.	SCLC	24	18 (75%)	08 - 74
10.	TC	04	01 (25%)	25 - 58
11.	Sarcoma	01	00	26

WD (well differentiated), MD (moderately differentiated), PD (poorly differentiated), SCC (squamous cell carcinoma), AdC (adenocarcinoma), NSCLC (non small cell lung carcinoma), LCLC (large cell lung carcinoma), SCLC (small cell lung carcinoma), TC (typical carcinoid), AC (atypical carcinoid), ACC (adenoid cystic carcinoma), MC (metastatic carcinoma).

Table 3: Morphological types of lung carcinomas in 26 female patients with different age groups and smoking history of >10 years.

Sr. No.	Morphology of lung carcinoma	Number of cases reported	No. of cases with +ve smoking history	Age range
1	MD SCC	01	00	62
2	MD SCC	03	02 (66%)	60 - 70
3	WD-AdC	03	00	12 - 56
4	MD-AdC	02	00	68 and 70
5	PD-AdC	04	01 (25%)	42 - 65
6	BACA	02	00	50 and 60
7	PD-NSCLC	01	01 (100%)	60
8	SCLS	02	01 (50%)	12 and 70
9	TC	02	00	32 and 56
10	AC	03	00	14 - 40
11	ACC	01	00	25
12	MC	01	00	25
13	Anaplastic	01	00	17

were strongly positive with HDC giving an intracytoplasmic granular pattern of staining (Fig. 2). The remaining 60% (n=06) large cell lung carcinomas which were negative for HDC, were strongly positive with Cyfra 21-1 (Fig. 3) along with the

sections of non small cell lung carcinomas and sarcoma, being strongly positive and negative respectively. All small cell lung carcinomas (Fig. 4), atypical and typical carcinoids were also strongly reactive to HDC immunostaining. Antimucin antibody was strongly positive (Fig. 5) and negative in each 02 of the 04 (50%) poorly differentiated adenocarcinomas where all of them were strongly reactive to Cyfra 21-1.

DISCUSSION

The present study not only assessed the clinicopathological pattern of lung carcinoma with respect to the seven above mentioned parameters but also justifies the use of immunohistochemistry in histopathological diagnoses and classification of lung cancer morphologically into neuroendocrine and non neuroendocrine carcinomas. The most prevalent lung carcinoma in males was non small cell lung carcinoma including squamous cell carcinoma. Most of them i.e 51% male patients were between the age group of 41-60 years. In contrast, adenocarcinoma was observed as the most prevalent malignancy in females with 58% being in the age group 51-70 years. Squamous cell carcinoma followed by small cell lung carcinoma were most commonly associated with smoking in both genders. Regarding the

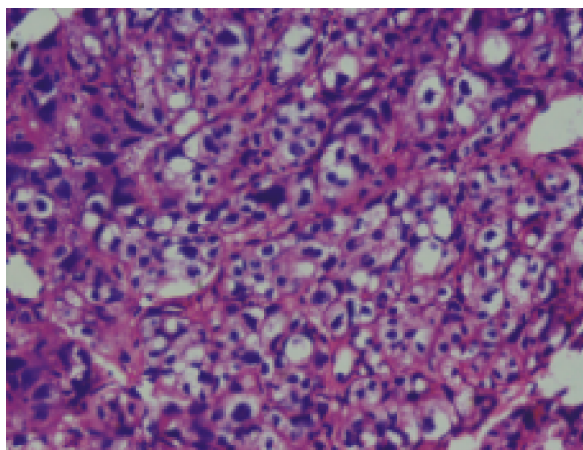


Fig. 1: H & E staining of large cell lung carcinoma.

gross location of lung carcinoma, left lung was involved in males 1.5 times the right lung whereas in females right lung was involved 2.5 times the left lung. Upper lobe was most frequently involved in both genders. The major symptoms were cough and/or expectoration (92%), dyspnoea (50%), haemoptysis (41%) and chest pain (84%). These were clinicopathological features of lung carcinoma are in accordance with reports from other studies conducted in tertiary care hospital settings.

Table 4: Gross location of lung malignancies in 116 males and 26 females.

	No. of Male Cases	Location in lung and Chest	No. of Female Cases	
RIGHT LUNG (44)	21	Upper Lobe	08	RIGHT LUNG (17)
	10	Lower Lobe	05	
	04	Middle Lobe	02	
	02	Mid-Lower Lobe	01	
LEFT LUNG (68%)	04	Whole Lobe	00	LEFT LUNG (07%)
	03	Chest wall	01	
	39	Upper Lobe	03	
	12	Lower Lobe	01	
	03	Middle Lobe	00	
	02	Mid-Lower Lobe	00	
	06	Whole Lobe	01	
	06	Chest wall	02	
OTHERS (04)	04	Including mediastinal, pleural, metastatic etc.	02	OTHERS (02)

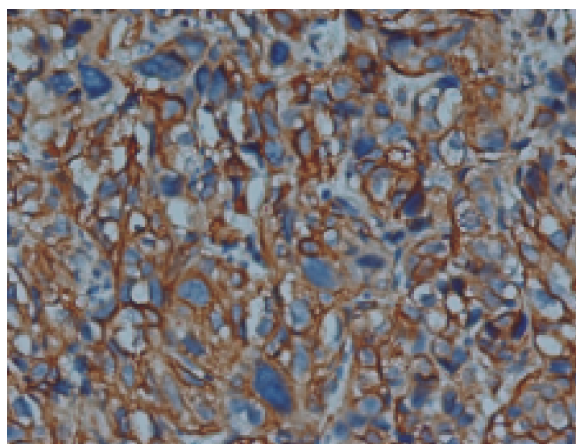


Fig. 2: HDC staining of large cell lung carcinoma.

According to Chandrashekhar, bronchogenic carcinoma is the most common cancer in Nepal. In a retrospective case-series analysis of 136 cases of primary bronchogenic carcinoma treated between September 2001 and August 2005 in a tertiary care hospital of western Nepal, the median age of the male and female patients was 67 and 66 years, respectively. The maximum number of patients was in the 60-69 year age group. One-hundred and thirteen (83.1%) of these patients were smokers. Among the male patients, 83.3% (60/72)

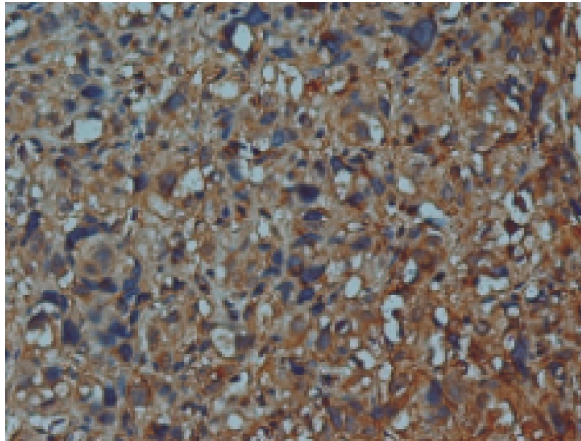


Fig. 3: *Cyfra 21-1 staining of the similar large cell lung ca.*

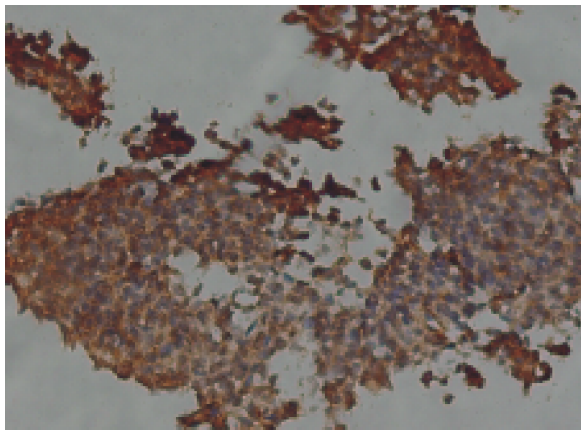


Fig. 4: *Small cell lung carcinoma showing positive staining w.*

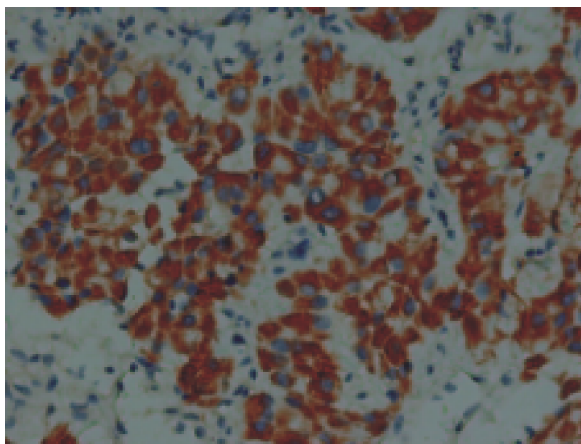


Fig. 5: *Poorly differentiated adenocarcinoma showing positive.*

were smokers and 82.8% females (53/64) were smokers. The male to female ratio of the patients

was 1.1: 1. The most common histological type was squamous-cell carcinoma (51.5%), followed by small-cell carcinoma (17.6%) and adenocarcinoma (8.1%)⁷. Similarly according to Pathak, patterns of lung cancer in India varies from the western population. The data from lung cancer clinic of a tertiary care hospital between 1999 and 2001 revealed that for 403 cases of lung cancer, peak incidence was in the age range of 51-60 years (mean 56.27 years). Overall male to female ratio was approximately 10:1. Among them 88% were smokers of which 91 percent were males and 50% females. Non small cell lung cancer constituted 80%; whereas small cell lung cancer was seen in 20%. Squamous cell carcinoma was reported to be the commonest variety (33.16%) in India as compared to adenocarcinoma in the west. The disease tends to occur early (the peak incidence was at 51-60 years)⁸.

In the present study, IHC was employed only for confirmation of diagnoses in some biopsies. An interesting finding in our patients was a strong positive staining of HDC in 04 of 10 large cell lung carcinomas, the histological (H & E) features reflected poor differentiation that could lead us to diagnose them as Non NEC origin. This raises the questions regarding the variable prognosis and the therapeutic modalities of the two different types of lung carcinoma. Histamine is produced by the enzyme HDC through the enzymatic decarboxylation of the histidine present in foods⁹. According to Sylvia et al. and Graff et al, the HDC stands in the forefront of the tumour markers destined to characterize the neuroendocrine origin of the tumours especially in cases of pulmonary neuroendocrine cell neoplasia.^{10,11} Our observations of the vigorous expression of the HDC in small cell and 04 large cell lung carcinomas and other related neuroendocrine carcinomas might be a step further in the biochemical characterisation of these frequent and malignant type of lung tumours. Cyfra 21-1 is currently identified as a polyclonal antibody IgG2 to the KS 19-1 and MB 19-21 epitopes of cytoskeleton formed by the CK 19¹² which is an acidic (type I) subunit with a low molecular weight i.e 40 kD¹³. Its reproducible and highly sensitive staining characteristics make Cyfra 21-1 a useful antibody to be applied as a broad epithelial marker for the detection of carcinoma in routinely processed paraffin sections¹⁴. Similarly the microscopic diagnosis of poorly differentiated mucinous adenocarcinomas was confirmed by utilizing antimucin antibody that was strongly positive in 02 and negative with only a few scattered cells being reactive in the remaining 02 carcinomas. The lung sarcoma was non reactive for Cyfra 21-1, affirming its epithelial specificity.

It is **concluded** that squamous cell and non small cell carcinomas were the most common pulmonary malignancies. Male was the dominant sex. History of smoking was positive in large majority (64.6%) of lung cancer. The commonest presenting complaint was cough and pain in chest. Immunohistochemistry was found to be a very useful modality to confirm the diagnosis of many cases where H&E stained sections do not help. Cyfra 21-1 is a broad epithelial tumour marker of choice, regardless of the origin of the epithelium and can be reliably employed to confirm the epithelial nature of malignancy. On the other hand, HDC is a preferred tumour marker for only neuroendocrine malignancies of the lung regardless of their degree of differentiation. Similarly, antimucin antibody can also be utilized for confirmation of mucinous differentiation even in poorly differentiated adenocarcinomas of lung.

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