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Research Article

Shifting trends of lung tumours and its diagnosis by lung biopsy: a study of 78 cases

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ABSTRACT

Background: The objective of the study was to study the spectrum of pathological lesions in patients with lung mass and to study correlation between clinical findings, histopathological pattern and immunohistochemical stains in various biopsy specimen for differentiation and typing of tumors.
Methods: This retrospective study was done for the period of three years at Department of Pathology, New Civil Hospital, Surat, India, which is a tertiary health care Centre. Here we studied 78 cases of lung biopsy received in formalin, which were subjected to histopathological examination. Immunohistochemistry was performed as and when required.
Results: Total 78 lung biopsy specimens were examined. Out of which, 59 cases (75.6%) were neoplastic, 12 cases(15.4%) were non-neoplastic and 7 cases (9%) were inconclusive. The commonest histological type of malignancy was adenocarcinoma which is associated with peripheral mass lesion, female gender and in non-smokers. Commonest non-neoplastic lesion was tuberculosis. Malignancy was seen quite common in patients presented with lung masses in our institute.
Conclusions: Lung tumours are quite common in patients presented with mass lesion. Similar to global trend, adenocarcinoma is the commonest histological type now and associated with change in incidence among women, in non-smokers, molecular alteration and prognosis which need further investigation. Immunohistochemistry is helpful in cases which are not accurately subtyped by histomorphology alone.

Keywords: Lung biopsy, Lung tumours, Histological types

INTRODUCTION

Management of an indeterminate pulmonary nodule is a diagnostic challenge that commonly confronts primary care physicians and specialists. Lung biopsy is a simple, relatively safe, rapid and reliable technique for the diagnosis of pulmonary mass lesions, particularly with the aid of computed tomography (CT) scan. Lung mass that persist or grow and larger than 3 cm should be biopsied if possible. Biopsy not only distinguishes between benign and malignant lesions but also helps in typing of lung cancer, so initiation of specific therapy like chemotherapy or surgery is possible without unnecessary delay.

Lung cancer is the most commonly diagnosed and fatal cancer annually since 1985 in the world. Worldwide, there are 1.61 million new cases of lung cancer per year, with 1.38 million deaths, making lung cancer the leading cause (28%) of cancer-related mortality.[1] In India, approximately 63,000 new cases of lung cancer are reported each year.[2] Adenocarcinoma is the most frequent

histopathological type of lung cancer and today it accounts for about 30-50% of all new lung cancer cases[3] and associated with peripheral location, increased incidence in women and in never smokers. Despite the modest improvements in treatments during the last few decades, the prognosis of lung cancer is still poor.

METHODS

This retrospective study was done for the period of three years at Department of Pathology, New Civil Hospital, Surat. Here we studied 78 cases of lung biopsy specimen of lung mass, received in formalin and were subjected to histopathological examination (H & E stain) and IHC stains(HMWCK, P53,TTF-1, CK-7, CK-20, Synaptophysin, Chromogranin, CD56) for further subtyping whenever required. Detailed case history was taken with clinical examination data and we studied correlation of histopathological patterns with age, gender, history of smoking, location, radiological findings, morphology and metastatic spread.

RESULTS

In present study of 78 cases of lung biopsy, 54 cases were males (69.2%) and 24 cases were females (30.8%) with a male to female ratio of 2.3:1.Age ranged from 5-85 years with majority of the cases were in fifth decade and sixth decade, 22 cases (28.2%) and 17 cases (21.8%) respectively, with peak in 5th decade and mean age of 50.2 years. CT guided biopsy accounted for 83.3% 965 cases) of the patients and rests were excision biopsy 10.3 % (8 cases) and bronchoscopy guided biopsy 6.4% (5 cases).

Majority of cases, 72% (56 cases) were centrally located and 28% (22 cases) were located peripherally.42 cases (54%) out of all the 78 cases were smokers in which 35 cases (45%) were associated with malignant lesion, 6 cases (7.7%) were inconclusive and 1 case (1.7%) was non-neoplastic.

In present study out of total 78 cases, 12 cases (15.4%) were non-neoplastic, 59 cases (75.6%) were neoplastic and 7 cases (9%) were inconclusive in the study. Among 12 non-neoplastic cases, 5 cases (42%) were tuberculosis, 3 cases (25%) were fungal infection and hydatid cyst each and 1 case (8%) was organizing pneumonia. In 5 cases (42%) of tuberculosis, mean age of presentation was 30 years, male outnumbered female (4:1), only one case was smoker and presents with symptoms of cough breathlessness and pain with radiologically detectable mass lesion. AFB stain was positive in all of the cases. In 3 cases (25%) of fungal infection, 2 cases were of zygomycosis and one case was of aspergillosis. Mean age was 40 years, non-smokers; immune compromised and fungal ball was present on radiography. In 3 cases (25%) of hydatid cyst, all were below 35 years age and presented with cystic mass.

A total 59 cases (75.6%) were neoplastic, out of which 1 case(1.3%) was benign (Solitary fibrous tumor of lung) and 58 cases(74.3%) were malignant. Among 58 malignant cases, most common diagnosis was carcinoma (NSCLC-SCLC), which accounted for 47cases (81%). Within NSCLC(70.7%), most common histology was adenocarcinoma 22 cases(38%) followed by squamous-cell carcinoma 13 cases(22.4%), large-cell neuroendocrine carcinoma 1 case(1.7%) and sarcomatoid carcinoma 1 case(1.7%). 4 cases(6.9%) were only typed as non-small cell carcinoma-NOS, further subtyping was not possible due to very tiny biopsy. Small-cell carcinoma accounted for 6 cases (10.3%) as shown in Table 1.

Distribution of different malignancy with location:

In 58 total malignant cases, 39 cases were centrally located and 19 cases were located peripherally. 10 cases (77%) of squamous cell carcinoma, 6 cases (100%) of small cell carcinoma and 11 cases (50%) of adenocarcinoma were located centrally in the present study. But in cases of peripheral mass lesion, chances of adenocarcinoma (58%) were more likely.

Gender difference between distributions of different malignancy:

In 58 malignant cases, 39 cases were male and 19 cases were female. Squamous cell carcinoma 12 cases (92%) and small cell carcinoma 4 cases (67%) were more commonly seen in male while in female, adenocarcinoma (58%) was more common subtype.

Smoking habit in relation to different malignancy:

35 cases were smoker and 23 cases were non-smoker in total 58 malignant cases in the present study. Squamous cell carcinoma (100%) and small cell carcinoma (67%) were associated with smoking while adenocarcinoma was more common in non-smokers (64%). In male smokers chances of squamous cell carcinoma (36.5%), adenocarcinoma (24.2%) and small cell carcinoma (9.1%) were in decreasing frequency. While in non-smokers, in male and female both, chances of adenocarcinoma were more, 49.9% and 64.7% respectively.

Immunohistochemistry findings:

Out of 58 malignant cases, result of tru cut biopsy was conclusive in 54 cases (93%) and proved to be inadequate for complete diagnosis in 4 cases (7%), in which primary panel or further IHC panels were required for further subtyping of malignancy. This was due to inadequate material of tru cut biopsy. IHC was performed on 8 cases of squamous cell carcinoma and all were positive for HMWCK. Out of 19 cases of adenocarcinoma, all cases were positive for CK-7, 84% cases were positive for TTF-1 and 16% cases were positive for CK-20. TTF-1

and CD-56 were positive in all cases of small cell carcinoma and NSE was positive in 75% of cases. Large cell neuroendocrine carcinoma expressed chromogranin and negative for CK-7, TTF-1, p63. Sarcomatoid carcinoma expressed CK, Vimentin, HMWCK (focal) and negative for CK-7, TTF-1 and Synaptophysin.

Table 1: Distribution of different malignant cases.

Morphology	No of cases	Percentage
Carcinoma(SCLC- NSCLC)	47	81%
Squamous cell carcinoma	13	22.4%
Adenocarcinoma	22	38%
Small cell carcinoma	6	10.3%
Large cell neuroendocrine carcinoma	1	1.7%
Sarcomatoid carcinoma	1	1.7%
Non small cell carcinoma, NOS	4	6.9%
Poorly differentiated malignancy	1	1.7%
Round cell tumour	3	5.1%
Spindle cell tumour(Low grade)	1	1.7%
Synovial sarcoma	1	1.7%
Lymphoma	2	3.4%
Hodgkin's lymphoma	1	1.7%
B cell NHL	1	1.7%
Metastasis	3	5.1%
Metastasis from spindle cell neoplasm(low grade fibrosarcoma)	1	1.7%
Metastasis from GI/pancreatic adenocarcinoma	1	1.7%
Metastasis from germ cell tumour	1	1.7%
Total	58	100%

DISCUSSION

Tissue sampling of a thoracic lesion is indicated when the diagnosis cannot be obtained by the non-invasive techniques and the diagnosis will modify the stage of the disease or influence the therapeutic strategy. Radiographic diagnosis can be useful, but it cannot accurately predict histology or whether a lesion is benign or malignant. Mass lesion in the lung is more likely to be malignant. Pretreatment biopsy of the primary tumor is essential for most patients presenting with lung masses. Lung biopsy can be performed by bronchoscopy guided biopsy, CT guided biopsy or excisional biopsy. A CT-guided percutaneous needle biopsy of the lung is commonly used as an outpatient diagnostic procedure and is relatively safe, sensitive and accurate method of diagnosing benign and malignant lesions as well as suitable for obtaining tissue samples of sufficient quantity and quality for allowing molecular analysis of biomarkers. Image-guided approaches also allow biopsy from areas of the tumour felt most likely to harbour viable tumour (i.e., avoiding centrally necrotic areas) and representative of whole tumour. Tru cut biopsy is very helpful in early diagnosis and less invasive as compared to excision especially to differentiate benign from malignant tumour and when oncosurgeon is planning pre-operative chemotherapy or in advanced disease and in small cell carcinoma where surgery is not recommended. A large field of research is going on for improving outcome in lung cancer.

Lung cancer is the leading cause of cancer-related death worldwide and being increasingly detected in India due to increased awareness about bronchogenic carcinoma and improved diagnostic techniques. In the management of lung tumours, accurate diagnosis, using a combination of clinical, radiographic and histological data is critical in optimizing outcome. In malignant tumour, first approach should be to classify tumour as small cell carcinoma (SCLC) or non- small cell carcinoma (NSCLC). The histological subtyping of non-small cell lung carcinoma in squamous cell carcinoma and adenocarcinoma is also important now because the therapeutic approaches, outcome, prognosis and survival differs greatly. In adenocarcinoma, several targetable molecular alterations as EGFR mutation, KRAS mutation and EML4-ALK rearrangements are identified. Targeted therapies hold a considerable promise in the treatment of patients with lung cancer.

The age range in the present study was 5 to 85 years with the peak in fifth decade, which was same as documented in recent studies.[4,5,6] The preponderance of male patients (69%) with male to female ratio of 2.3:1 in the present study, is comparable to that of other three recent studies i.e. 71.1%[7], 78.9%[5]and 80.6[8].In the present study of 78 cases,

75.6% cases (59 cases) were neoplastic, 15.4% cases (12 cases) were non-neoplastic and 9% cases (7 cases) were inconclusive.

Lung tumours were more common centrally (67.2%), which is comparable to Manickam et al study.[9] 45% cases were active smokers amongst malignant cases. This finding is similar to other studies.[6,10]

The present study and the study by Noronha et al[10] and Mondal et al [6] showed similar results with predominance of Adenocarcinoma followed by squamous cell carcinoma, small cell carcinoma and large cell carcinoma. Over the past four decades, there has been a shift in the pathologic distribution of NSCLC. Prior to the 1970s, squamous-cell carcinoma was the most common histological type of NSCLC. However, since about 1975, there has been a dramatic increase in the incidence of adenocarcinoma, making it the predominant histological subtype of NSCLC.[10,11] Thus far, not much information was available as to the distribution of the histological subtypes in India. A review article from 2004 stated that squamous-cell carcinoma was still the predominant histological subtype of NSCLC in India.[12] The incidence of adenocarcinoma was reported to be significantly higher than that of squamous cell carcinoma in recent studies by Tan et al[7] and Madan et al[13] Where as in certain other national and international studies, prevalence of squamous cell carcinoma was more than adenocarcinoma.[8] We found that adenocarcinoma accounts for 53.6% of NSCLC while only 31.7% were squamous-cell carcinoma. Results from present study, Noronha et al [10] and Mondal et al[6] study suggest that a pathologic shift may have occurred in India as well. There is change in concept regarding diagnosis of BAC, a variant of adenocarcinoma. Travis et al[14] in 2011 recommended discontinuing the term 'BAC' and it can be regarded as adenocarcinoma with lepidic growth with or without invasion.

When comparing the characteristics of the lung cancer cases, squamous cell carcinoma and small cell carcinoma was the predominant type of lung cancer among men but women were found to be more likely to have adenocarcinoma as compared to men and this was consistent with Kowski et al. (2010) and Radzikowska et al. (2002).The incidence of lung cancer began to increase in women in the early 1950s and is still increasing; in particular there has been a relative increase in adenocarcinoma [15]and there has been an increase in mortality among patients with adenocarcinoma over time.[16] In the present study, 100% of small cell carcinoma, 80% of squamous cell carcinoma and 50% of adenocarcinoma were centrally located but in patients presented with peripheral mass lesion (19 cases), 11 cases (57.9%) were of adenocarcinoma, which is similar to other study.[17]

All cases of squamous cell carcinoma and 67% of small cell carcinoma in the present study showed correlation with smoking which is similar to Noronha et al [10] and Mondal et al[6] study. In cases of adenocarcinoma, the present study (60.9%) and the study by Noronha et al [10] (44.8%) showed, it was more common in non-smoker than smoker. The strength of the association between cigarette smoking and lung cancer varies by cell type, with the largest for squamous and small cell carcinomas and somewhat smaller for adenocarcinoma.[18] 40% of the patients with lung cancer in our study were non-smoker. The major risk factor for developing lung cancer is tobacco use but the proportion of lung cancer in never-smokers is expected to increase as successful smoking prevention and cessation programmes are implemented. Although smoking-related carcinogens act on both proximal and distal airways inducing all the major forms of lung cancer, cancers arising in never-smokers target the distal airways and favour adenocarcinoma histology.[19] The increase in the incidence of adenocarcinoma was thought to be mainly attributable to a change in smoking pattern and an increased preference for filter cigarettes that have low tar, but high nitrate content.[23] Earlier studies reported that the increased incidence of adenocarcinoma was confined to smokers. In contrast, statistically higher occurrence of adenocarcinoma in non-smokers as compared to smokers was present. This was supported by other studies in the literature.[23] With the switch from unfiltered to filtered cigarettes, the depth of inhalation had been altered.[24] In particular, smoke from unfiltered strong cigarettes may be shallowly inhaled, resulting in chemical carcinogen deposition centrally in the bronchial area and giving rise to squamous cell carcinomas. Smoke from filtered milder cigarettes may be more deeply inhaled, resulting in carcinogen deposition more peripherally and giving rise to adenocarcinoma. Reducing the nicotine content may also promote deeper inhalation as smokers attempt to compensate. Recent studies suggest that the increase in adenocarcinoma is not solely due to a change in pattern of cigarette smoking, but must be due to non-smoking-related factors.[25,26]

There was significantly higher proportion of females among lung cancer patients who were non-smokers. This was consistent with findings noted in prior studies from Asia including China, Japan and Northern Indiawhere 65%, 70% and 94% of the lung cancer patients who were non-smokers were female. Lung cancer in never-smokers was associated with female gender,[20-22] lower median age at diagnosis, adenocarcinoma subtype, more advanced stage at presentation[20] and different molecular characteristics which suggest, it is distinct from the more common tobacco associated lung carcinoma and benefit from EGFR tyrosine kinase inhibitors.

Most NSCLCs are inoperable, and pathologic diagnosis is made only on small tissue samples that are prone to diagnostic inaccuracy. Primary screening with histopathological morphology is helpful in almost differentiating non-neoplastic and neoplastic cases and further typing of malignant tumours in most of cases, almost reaching a final diagnosis which is further confirmed by IHC but there are few cases where morphological subtyping of malignancy is not possible, necessitating a diagnosis of NSCLC-NOS.

Immunohistochemistry(IHC) associated markers could help predict the final subtype in NSCLCs, diagnosed as NSCLC-NOS by histological morphology alone with advantages of its remarkable sensitivity and specificity, its applicability to routinely processed, formalin fixed material, and compatibility to most common fixatives.

In case of squamous cell carcinoma in the present study, HMWCK and p63 were positive in all performed cases (100%) and TTF-1 were negative in all 8 cases (100%), which showed concordance with that of Rekhtman et al [27], Nicholson et al [28] and other study.[29-32] In case of adenocarcinoma, in the present study, CK-7 was positive in 100% cases, TTF-1 was positive in 84% of cases and CK-20 was positive in 16% of cases, which is in concordance to other studies.[29,33-35] In case of small cell carcinoma, the present study showed 100% positivity with CD-56 and TTF-1 and 75% with NSE, which is similar to other studies.[36-40]

CONCLUSION

Globally, there have been important changes in incidence trends among gender, histology and non-smokers. In past, Squamous cell carcinoma was most frequent subtype of lung cancer in India. But similar to global trend, pathological shift to adenocarcinoma may have occurred in India as well. Considerably higher numbers of Indian patients with lung cancer are non-smokers, which represents a distinct clinical entity with unique epidemiological, clinical and molecular characteristics of tumours which requires research and further refine treatment strategies for these group of patients.

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