DOI: 10.7860/JCDR/2019/40026.12757

Review Article

Pathology Section

Approach to Lung Neoplasm-Primary vs Metastasis: Short Review

NEEMA TIWARI

ABSTRACT

Lung cancer is a very serious problem of the Indian subcontinent, especially in the lower socioeconomic subgroups. As per the ICMR registry of 2002, in Indian population lung cancer is the 5th most common tumour and 2nd most common tumour in the males. It accounts for 6.9% of new cancer cases detected each year. Since lung is a metastatic site for almost all the cancers in the body there is a great confusion in diagnosing a primary from metastasis or pleural tumour. Hence, this short review aims to throw some light on the salient features and the approach. All pubmed indexed articles present online and in English were read and then summarised in this paper. There were many overlaps morphologically in pleural tumours, lung primary and metastasis and morphology apart IHC and molecular factors play a great role in its diagnosis as is discussed in the article.

Keywords: Diagnosis, Lung cancer, Mesothelioma, Methods, Pitfalls, Primary

INTRODUCTION

Lung cancer is a very serious problem of the Indian subcontinent, especially in the lower socioeconomic subgroups. As per the ICMR registry of 2002, in Indian population lung cancer is the 5th most common tumour and 2nd most common tumour in the males. It accounts for 6.9% of new cancer cases detected each year [1]. As per the national cancer registry programme in 2013 ICMR projected and estimated 11.49 lac cases of lung cancer in 2015 and around 17.3 lac cases by 2020 [2]. Recently it has been observed that Lung cancer deaths are declining in men, and the death rate in women has plateaued secondary to decrease in smoking. There are many aetiological factors involved in the genesis of a primary lung carcinoma like smoking active or passive, biofuel/biomass gas exposure, certain dyes in aerosol [3].

Another group of thoracic tumours apart from lung is the aggressive pleural malignancy, Malignant Pleural Mesothelioma (MPM). It is related to exposure to mineral fibers, particularly asbestos, with a latency period of approximately 40 years between fiber exposure and disease presentation [4,5]. It arises from the mesothelial lining of the pleura and requires morphological assessment and correlation with the clinical and radiologic findings, immunohistochemistry (IHC) and molecular tests (Next Generation Sequencing or NGS) which have been developed more recently.

The third group regarding lung lesions which raises a concern is the metastasis to the lungs which can mimic the primary lung tumours. This needs to be taken into consideration as lung is a metastasizing site for almost every tumour of the body. Infact it has been seen that a breast adenocarcinoma can be mistaken as lung primary or even a tubulopapillary pattern of mesothelioma, glycogen rich tubular pattern of mesothelioma can be mistaken for a lung primary adenocarcinoma or metastasis. Hence a big diagnostic dilemma for a practicing pathologist is the inability to identify the site of origin of neoplasms even in the era of advanced imaging techniques, immunohistochemistry, and molecular tests [6-8].

The pathological approach to lung lesions should always be based on mainly three points:

1) Age, sex and profession of the patient; 2) Radiological and clinical findings; and 3) Histopathology . The age and the sex of the patients gives us a pointer regarding the type of primary or metastasis that we can suspect and for which we can perform Immunohistochemistry (immunos) or IHC) and molecular factors and cytogenetic tests (impact). For example primary adenocarcinoma lung is seen commonly in non smokers and in Indian scenario the female population, while Squamous Cell Carcinoma (SCC) favours males who are the predominantly smokers in our Indian society, although in recent times this distinction has blurred as both males and females in urban and rural society smoke bidi, cigarettes or cigars or are exposed to biomass gas or fuel [9,10].

Clinical history is important to rule out metastasis from ovaries and breast in females and prostate and testis (although rare) in males. History won't be of much consequence in germ cell tumours except for the age. A history of working on ships or with asbestos for long is a big pointer for suspicion of mesotheliomas.

Radiologically a CT or an X-ray becomes important while making a diagnosis. For example multiple bilateral round lesions in lung a.k.a the cannon ball appearance generalised effusion or collapsed lung or mass points towards metastasis [11]. Loculated pleural effusion and septal thickening points towards a MPM. Even in a primary lung tumour whether the CT shows ground glass opacity or a solid lesion holds a lot of importance in diagnosing an Adenocarcinoma in Situ (AIS) or Minimally Invasive Adenocarcinoma (MIA) versus an invasive adenocarcinoma [12]. It is of great importance to note that these entities usually do not present with any clinical findings but are diagnosed on suspicion or even incidentally.

As a thoracic pathologist one should always advice the surgeon to submit touch imprints to cytology before submitting the biopsy however it is important to be gentle with the touch imprints or else the biopsy may yield nothing. Another important message to be conveyed to the surgeon is the adequacy of the specimen both for histopathology, cytology and molecular factors. One more thing to be kept in mind by the surgeon especially in the case of mesothelial tumours is that minimum five cores including the surrounding deeper tissue and muscle should be sampled to determine the extent of invasion of the tumour [13].

For any thoracic pathologist the most important finding is the gross and microscopy with help from the cytologist. Generally it is advisable to not make rare diagnosis or definitive pattern based diagnosis on a biopsy, for that a resection specimen is always preferred. For diagnosis on a biopsy specimen one needs to keep in mind the limited amount of specimen available hence one has to be judicious in the use of sections for IHC and molecular factors. Also, to be kept in mind here is the extreme urgency of reporting a

biopsy, as the resection and further management depends on what one finds on biopsy [13,14].

PRIMARY CARCINOMA LUNG

It is hence important to discuss a few salient points of lung primaries, metastasis and pleural tumours in brief.

Adenocarcinoma Lung

The recent WHO classification (2015) has made quite a few significant changes in the lung adenocarcinoma category which would not be explained in detail but highlight the important changes. WHO now has adenocarcinoma in situ and minimally invasive adenocarcinoma as well defined terms with specific diagnostic criteria's. WHO classification of lung tumour involves the tumour size cut-off and any evidence of invasion [15]. A size less than equal to 3 cm without any invasion, with predominantly non mucinous epithelium or lepidic pattern is classified as AIS while tumour less than equal to 3 cm in size but with a focus of invasion greater than equal to 5 mm with predominantly non mucinous cells, may be lepidic but without stromal desmoplasia, necrosis or Lymphovascular Invasion (LVI) is classified as MIA. A catch for inexperienced pathologists who may confuse atypical hyperplasia or simply reactive changes in alveoli to AIS is that the cell morphology in AIS is relatively monomorphic or one toned, not much pleomorphism can be seen when compared to AAH or reactive lung lesion. However it is always important to correlate findings with the CT findings to analyse the presence of solid foci in a ground glass lesion. Also frozen sections should be processed and IHC done whenever in doubt [16-18].

Frank adenocarcinomas of the lung can have various histological patterns. Histological subtypes of lung carcinoma give a pointer towards the prognosis of the tumour, e.g., Lepidic has good prognosis, papillary and acinar have intermediate prognosis micropapillary, solid, cribriform, poorly differentiated have poor prognosis [19]. In any carcinoma we have to mention the pattern percentage as the predominant pattern with other patterns mentioned only in 5% increments. An important point to remember in lepidic growth pattern is that to measure lepidic component.

If invasion present focally, it is easy to measure with a ruler the width of the invasion site; however in multiple invasions in a field one takes the tumour diameter and multiply it with the average percentage of the lepedic growth pattern. A point to mention here is that a greater than 3 cm tumour with lepedic pattern but with no invasion should be reported as suggestive of lepedic carcinoma/suspicious of lepedic carcinoma [20-22].

Another important thing to be kept in mind is the fact that a solid carcinoma is a adenocarcinoma or a squamous carcinoma with poorly differentiated features. Histomorphologically to differentiate a solid carcinoma and adenocarcinoma at least two high power field of greater than equal to five intra cytoplasmic vacuole/mucin containing cells should be seen [23].

Terms like clear cell and signet ring cell have been removed from the classification and they are just described as clear cell or signet ring cell changes. Mucinous cystadenoma has now been made a part of colloid carcinoma [24-26].

STAS (Spread Through the Airways) is a new histomorphological finding which indicate poor prognosis even in grade 1 adenocarcinomas. Tumour cells in clusters or singly found in the airspaces of normal surrounding alveoli suggest spread of tumour to surrounding area even when morphological evidence of infiltration like breach of alveoli wall etc., is not there. The reason behind this is still being researched upon [25].

When invasion is being considered another thing to be kept in mind in the recent times in presence of extratumoural vascular invasion which increases chances of metastasis and reflect poor prognosis [27].

The best method to differentiate between a MPM, metastasis and primary is molecular factors and IHC have been discussed later.

Squamous Cell Carcinoma

Not many changes have been proposed in the SCC as far as morphology goes. Histomorphologically keratinization and intercellular bridges between cells are the two most important diagnostic features. The cell of SCC has a well defined membrane. A few important points to be kept in mind are that presence of keratin is no more a prognostic parameter. A tumour with greater than 50% basaloid component is termed as a basaloid carcinoma irrespective of the keratinization [28]. The initial morphological classification of clear cell, papillary, solid have been removed and now only terms like keratinized, non-keratinized and with basaloid features if basaloid component less than 50% is used. Clear cell is no more a type of SCC instead it's described a tumour with clear cell features [28]. A diagnostic pitfall here is p16 positivity. Although not very specific marker yet a metastasis of p16 positive oropharyngeal carcinoma should always be ruled out. Another thing to be remembered is that many a times an adenocarcinoma may have squamoid cells. If adeno and squamous both components are present greater than 10% then a tumour can be labeled adenosquamous carcinoma. Here it is also to be remembered that adenocarcinoma and squamous carcinoma will be present as two distinct regions, rarely intermingling with each other. Of course when in confusion IHC and molecular factors markers will prove to be of great helpers [29,30].

Another important parameter which is being taken into consideration is the tumour budding in lung cancers. An article correlating tumour buds in SCC lung with prognosis considered three Infiltrative (IFN) patterns of tumour margin in lung, IFNa was broad based smooth tumour edge expanding into the surrounding stroma, IFNc was the actual budding and infiltration of either single cells or nests of at least 4 cells into the surrounding stroma (this numerical criteria varies from organ to organ) while IFNb was in between a and c [30].

Neuroendocrine Tumours (NET)

This group contains the Small Cell Lung Carcinoma (SCLC)- Pure and combined, Large Cell Neuroendocrine Carcinoma (LCNEC) and Carcinoids-Typical and atypical. To highlight the salient features morphologically and genetically, carcinoid is different from other two tumour groups. While usually LCNEC and SCLC are high grade, carcinoid is low grade. SCLC and LCNEC are more common in smokers as compared to a carcinoid. There may be epithelial component in SCLC or LCNEC. Mitosis 2-20/2 mm^2 and necrosis help in making a diagnosis of atypical carcinoid tumour [33].

While typical carcinoids are more common in the lung, the mediastinum has prevalence for atypical carcinoids. While a typical carcinoid has characteristic salt and pepper nuclei, no nucleoli, less than equal to 2 mitosis per 10 high power field and no necrosis, atypical carcinoid has 2-10 mitosis/10 high power field and focal necrosis present [34]. Carcinoids both typical and atypical exhibit an organotypic pattern and atypical carcinoid does not show much pleomorphism. However, one should keep in mind the fact that atypical carcinoids are prone to metastasize regionally. In some cases late metastasis as long as after 10 years have been seen in carcinoids so a long term follow-up is required. Another important feature for carcinoids is that carcinoid syndrome is more common in gastric lesions than lung. Important pitfalls one should keep in mind while diagnosing carcinoids is presence of DIPNECH (Diffuse Intrapulmonary Neuroendocrine Cell Hyperplasia) and tumour lets [35].

SCLC is specific to smokers and old age males probably 65 years. It can have separate or intermixed adenocarcinoma or squamous carcinoma element and is mainly central and very well responds to chemotherapy. It shows excess of nuclear moulding round to spindly coarse granular chromatin inconspicuous nucleoli scant cytoplasm and as is said 2-3 times the size of a lymphocyte. A very important point to note here is that a 10% cut-off for component is there only for presence of a large cell carcinoma in a small cell lung cancer to call it Small cell/large cell carcinoma combined. For other

components any percentage of adenocarcinoma or squamous carcinoma is a combined SCLC [36]. Brain metastasis is very important so prophylactic cranial irradiation is a must in SCLC [37].

LCNEC is diagnosed when the tumour has high grade features like necrosis geographic, mitosis and presence of cells resembling small cell but with clumpy chromatin, nucleoli present and moderate eosinophilic cytoplasm. It is a poorly differentiated tumour which could even be of a prior adeno or squamous origin so IHC is very important.

Large Cell Neuroendocrine Carcinoma (LCNEC)

It is safe to say that this diagnosis is more of exclusion. Basaloid carcinoma has become a subpart of SCC, lymphoepithelial tumours being classified into "others" and rests all the tumours being called as undifferentiated forms to be ruled out by IHC. LCNEC has been grouped under neuroendocrine tumours. Rhabdoid and clear cells which were initially cell types have now been removed and are mentioned as morphological features while reporting. If IHC give either a p40 or a TTF1 positive then a diagnosis of carcinoma favouring SCC or adenocarcinoma or a null phenotype when both negative will be rendered. Molecular tests show that an IHC positive adenocarcinoma and null phenotype show adenocarcinoma specific molecular pattern while a squamous marker positive on IHC shows a squamous signature on molecular testing [31,32].

Sarcomatoid Carcinoma

This is more of a resection diagnosis. The important points to remember are its types which can be a pleomorphic sarcoma with giant cells or spindle cells, a carcinosarcoma with epithelial elements with sarcoma and commonly found especially in young a pulmonary blastoma. These mostly confuse with metastasis of a spindle cell neoplasm from soft tissue or a spindle cell carcinoma etc., Pleomorphic sarcoma is now being seen as an extension of SCC or adenocarcinoma which has very poor differentiation due to presence of specific molecular markers [37].

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

The diagnosis of malignant mesothelioma depends on the clinical and radiological findings in conjunction with pleural fluid cytopathology and pleural biopsy. It is important to distinguish well differentiated epithelioid mesothelioma from reactive mesothelial proliferation, sarcomatoid or desmoplastic mesothelioma from reactive pleural fibrosis, and epithelioid mesothelioma from metastatic or pseudomesotheliomatous carcinoma, usually adenocarcinoma [38,39]. IHC has proven its utility in the past decade however despite many antibodies showing potential, it is generally agreed that no antibody shows absolute specificity or sensitivity for either of these tumour [40]. Therefore, each laboratory dealing with mesothelioma cases on a regular basis has developed its customised panel of antibodies for diagnosis [41,42].

Clinically an MPM encases the lung and might present with effusion. Radiologically, a very pertinent finding is loculated effusion and septal widening with or without infiltration. It is imperative in diagnosis of a MPM to have a deep adequate biopsy specimen for diagnosis. The ideal situation is to get a minimum of five biopsies which are large and deep sampling the parietal pleural and the surrounding soft tissue. An important feature to remember here is that sarcomatoid mesothelioma rarely sheds in the pleural fluid hence on cytology findings may reveal a negative pleural fluid diagnosis [43].

To histologically classify a MPM the three important types are: a) Epitheloid type; b) Sarcomatoid type; c) Biphasic or mixed [43,44]. Epithelioid morphology has cells with ample eosinophilic cytoplasm and hyperchromatic nuclei with inconspicuous nucleoli. The secondary patterns seen in a epithelioid MPM comprises of tubulopapillary, solid, trabecular, at times psammoma bodies may be present. A sarcomatoid type mimics fibrosarcomas, SFT or synovial sarcoma. The biphasic pattern has 10% of each sarcomatoid and epithelioid component. Another important MPM which is a diagnostic pitfall is the Desmoplastic MPM which has pattern less bands of dense collagen and mimics benign fibrous pleuritis or a stromal nodule [45,46].

Some rare types seen are micropapillary, adenomatoid, microcystic, clear cell, transitional, deciduoid, Small cell lymphohistiocytic, pleomorphic. The deciduoid, pleomorphic and sarcomatoid are the prognostically poor MPM's [47].

METASTASIS

The need to diagnose the site of origin of metastatic neoplasms has lead to development of variety of IHC tests and molecular methods. However, these ancillary methods cannot entirely substitute the information provided by careful examination of haematoxylin-eosin-stained histologic slides with careful clinical correlation [47,48].

We need to approach any suspected case of metastasis systematically beginning with the clinical details like age, sex, addictions, work environment any exposure to dyes, radiation, asbestos, smoker, non-smoker, etc. Then come the radiological or imaging studies for example in a lung primary we see for ground glass opacities (favouring an AIS/MIA) over solid nodule, or pneumonia like pattern common for mucinous adnocarcinomas, multiple intrapulmonary mets with military spread which can confuse with a miliary Tuberculosis or at times a cannon ball metastasis of lung. Then comes the gross pathology, type of tumour cell, tumour pattern and IHC. Grossly a dirty variegated tumour can be an yolk sac tumor, embryonal carcinoma, a pigmented black surface could be a melanoma, tan or golden yellow tumour could be renal or adrenocortical carcinoma. Consistency of the metastasis can also give a hint towards the primary site of the tumour. Fish flesh consistency is common in lymphomas and sarcomas. Hard consistency or large areas of calcification points towards a bony met while a soft mucinous tumour has lots of mucin, myxoid tumours can be cartilaginous or other myxoid sarcomas [49-52].

Microscopically, a tumour with mucin can be a primary invasive mucinous lung carcinoma or a met from pancreas and upper GIT. Mets from colorectal carcinomas have a lot of dirty necrosis, breast adenocarcinoma can cause lots of confusion with a primary lung, prostate and renal have a more blander cell morphology and clear cytoplasm, oncocytic tumours can be renal origin, adrenocortical or neuroendocrine, lymphomas can be confused with small cell tumours as far as morphology goes. Presence of pigment in a tumour might point towards melanoma. Presence of a cigar shaped nuclei and dirty necrosis is a colorectal carcinoma, spindle cells could be a primary lung soft tissue tumour or metastasis from sarcoma. Sometime neuroendocrine tumours also have a benign spindled morphology. Herein, lies the role of IHC and molecular factors [Table/Fig-1] [53-55].

IMMUNOHISTOCHEMISTRY, MOLECULAR FACTORS AND CYTOGENETICS

Discussing in brief the various immunostains and molecular factors used in primary lung cancer we know that the important stains which one has to perform to confirm a diagnosis is TTF1 and Napsin A in adenocarcinoma lung while p40 and p63 is useful to diagnose SCC. One combines the findings with the molecular factors results of Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK1), and off-late ROS, RET, K-Ras which are diagnostic as well as prognostic. These molecular mutation or driver mutations enable targeted therapy of the cancer. There are EGFR inhibitors being used for treatment from first generation to third generation drugs have been used and now antibody is being tested on cancer cells. Mutation of exon 19 and 20 is the most common to be studied to assess resistance or response to EGFR inhibitors. ALK positivity also is a good response indicator. Small molecules selectively inhibiting

Name	Morphology/Pattern	IHC	Molecular factors
Lung Adenocarcinoma	Lepedic, papillary, acinar, mucinous, micropapillary, cribriform, solid	**TTF-1** (nuclear, SPT24 and 8G7G3, transcription factor, positive in other tumours like thyroid), **NapsinA** (SCC 26%, coarse granular positvity)	EGFR (exon19,20), ALK/EML4, ROS, PDL1, K-RAS, BRAF
Lung squamous cell carcinoma	Keratinising, nonkeratinising, basaloid	CK5/6, p 63, p 40 (SPECIFIC), p16 neg if not mets from oropharynx or SCC	ROS, PD-L1, **K-RAS**
Lung-net	Carcinod/SCLC/ LCNEC	CD56, Chromogranin A, Synaptophysin, INSM-1	**ASCL1**, RAF/MEK/ERK, mTOR
MPM	Epithelioid, Sarcomatoid, Biphasic, Desmoplastic	Calretenin, Mesothelin, BAP-1, MTAP, WT-1	**P16, BAP-1**
Sarcomas	Synovial Sarcoma, SFT	CD34, CD99, EMA, STAT6 (nuclear)	SSX18-SSX1/2
Breast	Trabecular or cribriform architecture Comedo necrosis, Modest nuclear atypia	ER/PR/HER2/**GATA3**/GCDFP15 (GATA 3-urothelal ca, cholangioca, chorioca, chromophobe rcc)	BRCA1/2, triple negative, p53, ER/PR/Her2
Thyroid	Papillary features Nuclei with pseudoinclusions, nuclear clearing, and/or membrane folds Follicles with colloid	TTF1, thyroglobulin	RET, BRAF, KRAS, PPAR GAMMA
Prostate	Small monomorphic glands prominent nucleoli, Lack of mucin secretion	**PSA** (cytoplasmic granular), **PSAP** (cytoplasmic granular), PSMA (not specific in prostate cytoplasmic+membranous), **Prostein** (p501S, perinuclear) AMACR (not specific), p63 (absent in benign also)	PTEN-AKT altered, p53, TMPRSS2-ERG, SPINK-1 overexpressed CDH-1 deleted AURKA-MYCN amplified SPOP mutated
Pancreas	Mucin secretion glands lined by tall columnar cells	**Maspin, placental S100 (S100P) and IMP3** p53 expressed in most cases CK7, CK8, CK18, CK19, MUC1, MUC3, MUC4, **MUC5AC, CEA, B72.3, CA19-9, CA125 (48%)**	kras, CDKN2A4, p53, SMAD4, Her2 (50%)
Colorectal	Glands lined by pseudostratified columnar cells "Cigar-shaped" nuclei "Dirty" necrosis	CDX 2, CK 20, CK7 in rectal adenocarcinomas	Beta Catenin-Wnt (APC) MMSI BRAF
Stomach	Mucin secretion Signet ring cells	CK7, CDX2	c-Met: 20 - 40% in both intestinal and diffuse types APC: 30 - 40% in intestinal type, < 2% in diffuse type K-RAS: 1 - 28% in intestinal type, < 1% in diffuse type HER2 / ERBB2: 5 - 15% in intestinal type, < 1% in diffuse type p53: 25 - 40% in intestinal type, 0 - 21% in diffuse type
Sarcomatoid	Spindle cell lesion, poorly differentiated pleomorphic rhabdoid cells,	Vimentin, CD 34, STAT6 negative for CK5/6	Specific for tumour
Lymphomas	Small round blue cell, pleomorphism in high grade lymphomas	CD45, CD 20, CD3, Ki67, MUM1, CD 138, CD10, bcl6, bcl2 EBER-Lymphomatoid granulosis lung	-do-

[Table/Fig-1]: IHC and molecular factors.

k-ras G12C, a poor prognostic mutation and immune check point inhibitors are also being used. PD-L1 is another marker being studied from the point of better immunotherapy response in tumours which have that mutation [56].

P63, p40 are two very important stains to diagnose SCC where p40 is most specific, CK5/6 can be done for epithelial tumours. An important caveat to remember is to confirm the absence of EGFR or ROS etc on IHC by performing a FISH always [56].

The neuroendocrine tumours including SCLC have a marker panel of CD56, Chromogranin A, Synatophysin and off late another marker INSM1 is being used which gives nuclear staining and is a very specific stain for neuroendocrine tumours. CD 56 can stain macrophages and at times epithelial elements too. Another gene being studied in great detail in specially SCLC is ASCL-1 which encodes Basic Helix-Loop-Helix (BHLH) family of transcription factors. It is also being studied in medullary thyroid carcinomas [57]. One important point to remember is that presence of a morphological neuroendocrine area in a NSCLC, which is not proven on IHC, the pathologist should label the tumour adeno/squamous with neuroendocrine features and in tumours NSCLC, with positive IHC we should label it as NSCLC with neuroendocrine differentiation. In a large cell neuroendocrine morphology with negative IHC the pathologist it is LCNEC with NEM (Morphology) while in positive IHC the term neuroendocrine differentiation should be used [56].

Coming to mesothelial tumours, few common IHC markers used here are Mesothelin which is a GPI linked surface protein seen in aggressive mesotheliomas with poor outcome. Another marker WT-1 is not very specific in MPMs. MTAP or methyl adenosine phosphorylase (9p21 deletion) and BAP-1 help in differentiating a benign mesothelial proliferation from malignant. It is recommended to do pancytokeratin or more specific ones like CAM5., 2 plus 2 mesothelioma markers plus to metastasis panel. Except for sarcomatoid mesothelial carcinoma CAM 5.2 is expressed in all other MPM's. Other markers are calretenin which is cytoplasmic marker important in calcium utilisation for skeletal movement by cells, podoplanin which are not sensitive and can be absent giving rise to a Null phenotype [57,58].

IHC for mets has been given in [Table/Fig-1]. Ber EP4 a membranous marker important for epithelial origin, Claudin 4, MOC 31, GATA 3, PAX8 etc., are important markers for mets. Albumin ISH for HCC and intrahepatic CholangioCarcinoma, p16 and HPV-ISH for mets from oropharyngeal or cervical SCC are just a few examples to know [59,60].

CONCLUSION

Metastatic tumours are very common in the lung and hence the differential diagnosis of a lung primary or even a pleural primary entails almost all the tumours occurring in our body. Also, to be kept in mind is that lung metastasizes to brain, bone, and breast rarely to adrenals. In both situations a balance between IHC and morphology as both have their pitfalls helps pathologists to reach a diagnosis.

REFERENCES

[1] Salama R, Tang J, Gadgeel SM, Ahmad A, Fazlul H, Sarkar. Lung cancer stem cells: Current progress and future perspectives. Jour. of Stem Cell Research and Therapy. 2012;S7:007.

[2] Behera D. Epidemiology of lung cancer-Global and Indian perspective. JIACM. 2012;13(2):131-37.

[3] Malik PS. Lung cancer: Prevalent trends and emerging concepts. Indian J Med Research. 2015;141:5-7.

[4] Jensen AR, Mainz J, Overgaard J. Impact of delay on diagnosis and treatment of primary lung cancer. Acta Oncol. 2002;41:147-52.

[5] Lam S, NacAulay C, LeRiche JC. Detection and localization of early lung cancer by flouresence bronchoscopy. Cancer. 2000;89:2468-73.

[6] Pham PV, Nguyen ST, Phan NL-C. Roles of CD44 in stem cells and cancer stem cells. Onco Targets and Therapy. 2011:71-78.

[7] Ren F, Sheng W-Q, Du X. CD133: A cancer stem cells marker, is used in colorectal cancers. Worlds J Gastroenterol. 2013;19(17):2603-11.

[8] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer, 2015.
[9] Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology. 3rd ed. Geneva: World Health Organization (WHO), 2000.
[10] Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC. Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC, 2004.
[11] World Health Organization. Histological typing of lung tumours. Geneva: World Health Organization, 1967.
[12] World Health Organization. Histological typing of lung tumours. Geneva: World Health Organization, 1981.
[13] Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E, in collaboration with LHS, Countries pf. Histological typing of lung and pleural tumours. Berlin: Springer, 1999.
[14] Travis WD, Brambilla E, Noguchi M. The new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification. J Thoracic Oncol. 2011;6:244-85.
[15] Nivolumab approved for lung cancer. Cancer Discov. 2015;5:OF1.
[16] Lindeman NI, Cagle PT, Beasley MB. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists. International Association for the Study of Lung Cancer, and Association for molecular pathology. Arch Pathol Lab Med. 2013;137(6):828-60.
[17] Gustafsson BI, Kidd M, Chan A, Malfertheiner MV, Modlin IM. Bronchopulmonary neuroendocrine tumours. Cancer. 2008;113(1):5-21.
[18] Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treat Rev. 2009;35(3):228-36.
[19] Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumours of the diffuse neuroendocrine system. Curr Opin Oncol. 2008;20(1):1-12.
[20] Powell JM. Metastatic carcinoid of bone: report of two cases and review of the literature. Clin Orthop Relat Res. 1988(230):266-72.
[21] McCaughan BC, Martini N, Bains MS. Bronchial carcinoids: review of 124 cases. J Thorac Cardiovasc Surg. 1985;89(1):8-17.
[22] Travis WD, Brambilla E, Noguchi M. Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med. 2013;137:685-705.
[23] Kadota K, Nitadori J, Rekhtman N, Jones DR, Adusumilli PS, Travis WD. Reevaluation and reclassification of resected lung carcinomas originally diagnosed as squamous cell carcinoma using immunohistochemical analysis. Am J Surg Pathol. 2015;39(9):1170-80.
[24] Rekhtman N, Paik PK, Arcila ME. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung:lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res. 2012;18:1167-76.
[25] Kadota K, Villena-Vargas J, Yoshizawa A. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol. 2014;38:448-60.
[26] Shimada Y, Ishii G, Hishida T, Yoshida J, Nishimura M, Nagai K. Extratumoural vascular invasion is a significant prognostic indicator and a predicting factor of distant metastasis in non-small cell lung cancer. Journal of Thoracic Oncology. 2010;5(7):970-75. DOI: 10.1097/JTO.0b013e3181dd1803
[27] Lee HY, Choi YL, Lee KS. Pure ground-glass opacity neoplastic lung nodules: histopathology, imaging, and management. AJR Am J Roentgenol. 2014;202:W224-33.
[28] Isaka T, Yokose T, Ito H. Comparison between CT tumour size and pathological tumour size in frozen section examinations of lung adenocarcinoma. Lung Cancer. 2014;85:40-46.
[29] Naidich DP, Bankier AA, MacMahon H. Recommendations for the management of subsolid pulmonary nodules detected at CT: A statement from the Fleischner Society. Radiology. 2013;266:304-17.
[30] Masuda R, Kijima H, Imamura N, Aruga N, Nakamura Y, Masuda D. Tumour budding is a significant indicator of poor prognosis in lung squamous cell carcinoma patients. Molecular Medicine Reports. 2012;6:937-43.
[31] Kadota K, Yeh YC, Sima CS. The cribriform pattern identifies a subset of acinar predominant tumours with poor prognosis in patients with stage I lung adenocarcinoma: a conceptual proposal to classify cribriform predominant tumours as a distinct histologic subtype. Mod Pathol. 2014;27:690-700.
[32] Mackinnon AC Jr, Luevano A, de Araujo LC, Rao N, Le M, Suster S. Cribriform adenocarcinoma of the lung: clinicopathologic, immunohistochemical, and molecular analysis of 15 cases of a distinctive morphologic subtype of lung adenocarcinoma. Mod Pathol. 2014;27:1063-72.
[33] Fink G, Krelbaum T, Yellin A. Pulmonary carcinoid: Presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. Chest. 2001;119(6):1647-51.
[34] Scott WJ. Surgical treatment of other bronchial tumours. Chest Surg Clin N Am. 2003;13(1):111-28.
[35] Beasley MB, Thunnissen FB, Brambilla E. Pulmonary atypical carcinoid: predictors of survival in 106 cases. Hum Pathol. 2000;31(10):1255-65.
[36] Ferolla P, Daddi N, Urbani M, Semeraro A, Ribacchi R, Giovenali P, et al. Tumourlets, multicentric carcinoids, lymph-nodal metastases, and long-term behavior in bronchial carcinoids. J Thorac Oncol. 2009;4(3):383-87.
[37] Merrill RM, Henson DE, Barnes M. Conditional survival among patients with carcinoma of the lung. Chest. 1999;116(3):697-703.
[38] Harlamert HA, Mira J, Bejarano PA. Thyroid transcription factor-1 and cytokeratins 7 and 20 in pulmonary and breast carcinoma. Acta Cytol. 1998;42:1382-88.
[39] Bejarano PA, Baughman RP, Biddinger PW. Surfactant proteins and thyroid transcription factor-1 in pulmonary and breast carcinoma. Mod Pathol. 1996;9:445-52.
[40] Di Loreto C, Puglisi F, Di Lauro V, Damante G, Beltrami CA. TTF-1 protein expression in pleural malignant mesotheliomas and adenocarcinomas of the lung. Cancer Lett. 1998;124:73-77.
[41] Sadler JE. Thrombomodulin structure and function. Thromb Haemost. 1997;78:392-95.
[42] Yamada T, Jiping J, Endo R, Gotoh M, Shimosato Y, Hirohashi S. Molecular cloning of a cell-surface glycoprotein that can potentially discriminate mesothelium from epithelium: its identification as vascular cell adhesion molecule 1. Br J Cancer. 1995;71:562-70.
[43] Ordonez NG. Value of antibodies 44-3A6, SM3, HBME-1 and thrombomodulin in differentiating epithelial pleural mesothelioma from lung adenocarcinoma. Am J Surg Pathol. 1997;21:1399-408.
[44] Ordonez NG. The immunohistochemical diagnosis of epithelial mesothelioma. Hum Pathol. 1999;30:313-23.
[45] Clover A, Oates J, Edwards C. Anti-cytokeratin 5/6: A positive marker for epithelioid mesothelioma. Histopathology. 1997;31:140-43.
[46] Ordonez NG. Mesothelioma with rhabdoid features: An ultrastructural and immunohistochemical study of 10 cases. Mod Pathol. 2006;19(3):373-83.
[47] Galateau-Salle F, Brambilla E, Cagle PT. Pathology of Malignant Mesothelioma. London, United Kingdom: Springer-Verlag; 2006.
[48] Mangano WE, Cagle PT, Churg A, Vollmer RT, Roggli VL. The diagnosis of desmoplastic malignant mesothelioma and its distinction from fibrous pleurisy: a histologic and immunohistochemical analysis of 31 cases including p53 immunostaining. Am J Clin Pathol. 1998 Aug;110(2):191-9.
[49] Roggli VL, Kolbeck J, Sanfilippo F, Shelburne JD. Pathology of human mesothelioma: etiologic and diagnostic considerations. Pathol Annu. 1987;22(pt 2):91-131.
[50] Roggli VL. Human disease consequences of fiber exposures: A review of human lung pathology and fiber burden data. Environ Health Perspect. 1990;88: 295-303.
[51] Churg A, Colby TV, Cagle P. The separation of benign and malignant mesothelial proliferations. Am J Surg Pathol. 2000;24(9):1183-200.
[52] Greco FA, Hainsworth JD. Introduction: Unknown primary cancer. Semin Oncol. 2009;36(1):6-7.
[53] Seve P, Mackey J, Sawyer M. Impact of clinical practice guidelines on the diagnostic strategy for carcinomas of unknown primary site: A controlled 'before-after' study. Clin Oncol (R Coll Radiol). 2008;20(8):658-59.
[54] Hammar SP. Metastatic adenocarcinoma of unknown primary origin. Hum Pathol. 1998;9(12):1393-402.
[55] Park SY, Kim BH, Kim JH, Lee S, Kang GH. Panels of immunohistochemical markers help determine primary sites of metastatic adenocarcinoma. Arch Pathol Lab Med. 2007;131(10):1561-67.
[56] Tamboli P, Mohsin SK, Hailemariam S, Amin MB. Colonic adenocarcinoma metastatic to the urinary tract versus primary tumours of the urinary tract with glandular differentiation: A report of 7 cases and investigation using a limited immunohistochemical panel. Arch Pathol Lab Med. 2002;126(9):1057-63.
[57] Amin MB, Tamboli P, Javidan J, Stricker H, Venturina M, Deshpande A, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: An experience of 405 cases. Am J Surg Pathol. 2002;26(3):281-91.
[58] Campos S, Davey P, Hird A, Pressnail B, Bilbao J, Aviv RI, et al. Brain metastasis from an unknown primary, or primary brain tumour: A diagnostic dilemma. Curr Oncol. 2009;16(1):62-66.
[59] Gebauer GP, Farjoodi P, Sciubba DM. Magnetic resonance imaging of spine tumours: Classification, differential diagnosis, and spectrum of disease. Bone Joint Surg Am. 2008;90(suppl 4):146-62.
[60] Klempner SJ, Ignatius Ou SH, Costa DB. The clinical use of genomic profiling to distinguish intrapulmonary metastases from synchronous primaries in non-small-cell lung cancer: A mini-review. Clin Lung Cancer. 2015;16(5):334-339.e1.

PARTICULARS OF CONTRIBUTORS:
1. Resident, Department of Clinical Hematology, King George's Medical University, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Neema Tiwari,
5/69, Vinay Khand, Gomti Nagar, Lucknow, Uttar Pradesh-226010, India.
E-mail: drnt27.nt@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct, 19, 2018**
Date of Peer Review: **Dec, 07, 2018**
Date of Acceptance: **Jan, 25, 2019**
Date of Publishing: **Apr 01, 2019**