Abstract

Background and Aims: Advent of personalised treatment needs correct diagnosis of lung adenocarcinoma with its molecular subtyping. Minimal use of special stain or immunohistochemistry (IHC) in small specimens save material for molecular testing. Various histologic patterns in adenocarcinoma (ADC) subtypes have different prognostic implications and current recommendation is to describe these patterns in small specimens. Aim of this study was to diagnose adenocarcinoma from cytology specimens depending on adenocarcinoma pattern on fine needle aspiration smears and cell blocks. We also studied the additional role of cell blocks as a platform for special stain and IHC. Materials and Methods: Conventional smears and cell block (CB) preparation were examined from transthoracic CT guided FNA samples of suspicious lung malignancy cases. Clear defining architectural pattern and cytomorphological features in favour of adenocarcinoma were evaluated and mucin stain and IHC were used as and when required. Results: A total of 86 cases were included in this study, of which 83 cases were diagnosed as adenocarcinoma, 52 (62.5%) showed clear cut evidence of adenocarcinoma from smears and CBs. CB morphology alone aided the diagnosis in 12. Various ADC patterns in combination or alone were appreciated in these 64 cases. Sixteen needed mucin stain and 3 needed IHC for diagnosis. Forty one were ADC with solid pattern of which 39 showed high nuclear grade. Conclusion: Adequately cellular FNA smears and corresponding cell blocks of optimal quality can aid effectively in diagnosing adenocarcinoma and appreciating its pattern. Therefore, it would minimize the need for special stain and/or IHC with preservation of more material for molecular testing.

Keywords: Adenocarcinoma lung, adenocarcinoma pattern, cell block, FNAC

INTRODUCTION

Lung carcinoma is still the leading cause of cancer related mortality worldwide. Increasing incidence of adenocarcinoma overrides other histologic types. The emerging concept of genetic abnormality as one of its important risk factors amongst the never smokers and increasing incidence even in smokers have made its diagnostic work up a challenging issue. Selection of drugs against specific molecular target to personalize treatment strategies needs tumour subtyping based on newer techniques like immunohistochemistry (IHC) and molecular biology. New imperative for the pathologists to subtype adenocarcinoma was further emphasized by the observation that EGFR mutation and ALK, ROS 1 rearrangement are found primarily in adenocarcinoma. Molecular testing for detection of these genetic changes is now recommended in tumors classified as adenocarcinoma and in cases of non-small cell carcinomas (NSCC) where adenocarcinoma pattern cannot be excluded.

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Association for the study of Lung Cancer/American Thoracic Society/European respiratory Society (IASLC/ATS/ERS) classification of pulmonary adenocarcinoma (ADC) proposed in 2011 recognized 5 major patterns that should be used in classification of lung ADC.\[1\] They are Lepidic, Acinar, Solid, Papillary and Micro papillary patterns and subtype variants such as Mucinous, Colloid, Fetal and Enteric. The guidelines recommended subclassifying ADC on surgical resection specimens according to predominant pattern. Predicting the grade of adenocarcinoma depending on single most predominant pattern appears to be simple and sufficient. Various somatic genetic alteration in tyrosine kinase are characterised by different unique clinico-pathological profiles including histomorphological pattern of adenocarcinoma.\[4\]

There are growing number of studies of resected lung adenocarcinomas that have demonstrated its utility in identifying significant prognostic subsets and molecular correlation according to predominant pattern.\[5‑9\] As two-third of lung cancer patients present in advanced stages; their diagnosis is usually made on small biopsy or cytology specimens. Detection of cancers in early stage during screening is also based on limited specimen. Thus, small biopsy or cytology specimens may represent the only material available for diagnostic interpretation in a substantial numbers of cases. As per the guidelines of American College of Chest Physicians minimal invasive diagnostic technique should be used as first line test.\[10\] Thus, the target of specimen is shifting from being histology to cytology. The utility of cell block (CB) study in addition is appreciated largely owing to the significant role they play in preservation of architectural pattern and tumor cells representation for molecular genetics. Small tissue fragments obtained by effective chiselling during the process of FNA appear as “mini biopsies” and are useful in pattern recognition for further sub-classification.\[11\]

Different histomorphologic patterns observed in adenocarcinoma subtypes may produce additional prognostic information, on the assumption that they are functional phenotypes reflecting an underlying genotype.\[12\] Although IASLC/ATS/ERS classification 2011 has recommended to describe identifiable patterns in small biopsy/cytology specimens, the studies describing cytologic criteria of different histologic patterns of lung adenocarcinoma are limited. The difficulty in appreciating pattern may be related to lack of available established cytologic criteria, the overlap in some features and lack of experiences in defining specific pattern of ADC. The problem in applying IASLC/ATS/ERS classification are however not limited to cytology alone but also seen in small biopsy because of poor reproducibility. The study conducted by Rodriguez et al.\[13\] describing characteristic cytologic features including cytomorphology of FNAC smears and specially CB morphology with matched histology demonstrating single pattern, had provided some insight.

This current study was aimed at diagnosing ADC mostly on cytomorphology and pattern based approach in a resource constraint setup from FNAC smears and corresponding CB morphology. The CBs were used as a platform for mucin stain and IHC. Along with this, the different identifiable morphologic patterns were described. Nuclear grades and other associated background features were also evaluated.

**Methods**

This retrospective observational study was conducted on the archival cases of our institution that had undergone transthoracic CT guided FNAC and subsequent CB preparation for clinical and radiological suspicion of neoplastic pathology of lung. The study period was from February 2017 to January 2019. The study was approved by the Institutional Ethics Committee and informed consents were taken from all the patients. The simple and cost-effective method adopted for aspiration and subsequent smears and cellblock preparation has already been described by our group in earlier publications.\[14,15\]

Inclusion criteria followed for selection of the cases were:

1. Cases whose clinical and radiological features were available
2. Availability of adequately cellular smears and cellblocks of optimal quality
3. The cases which were suspected as adenocarcinoma on the basis of cellular features of FNAC smears.

All the cases with inadequate clinical and radiological features were excluded from the study.

Cytology smears stained with May Grunwald Geimsa (MGG) and Papanicolau (Pap) and cellblocks underwent formalin fixation, routine processing and paraffin embedding (FFPE) and Haematoxylin and Eosin (H&E) staining of the cases included in this study were reviewed by 4 experienced pathologists of our group. Consensus opinion was formed to allocate the cases.

Presence of architectural pattern and cellular features described as clear expression of adenocarcinoma differentiation by Travis et al.\[16\] for small biopsy and cytology specimens were considered as diagnostic criteria of ADC.

The various architectural patterns of ADC were cohesive clusters with acinar structures, pseudo papillae, true papillae, picket fence appearance and three-dimensional (3D) cell ball formations. The individual tumor cells showed foamy or vacuolated (translucent) cytoplasm and nuclei often situated eccentrically with chromatin ranging from finely granular, uniform to hyperchromatic and nucleoli being mostly large and single. Cases with cytology smears showing inconspicuous or absent clear defining architectural pattern of ADC but the cell blocks (CBs) sections having that ADC pattern were also considered as ADC.

The cases with cellular features in favour of ADC but absent clear defining ADC pattern were confirmed by periodic acid-Schiff with diastase stain (D-PAS) on CB sections. Those showing negative or rare and weak positivity were submitted
for IHC (Napsin-A, prediluted, mouse monoclonal, clone MRQ-60, Cellmarque – USA). Napsin positive cases were diagnosed as ADC, negative cases were submitted for IHC for squamous markers (p63, prediluted, mouse monoclonal, clone DAK - p63, DAKO – USA) as workup for further categorization.

Total number of ADC cases was then taken for describing different ADC patterns which were tabulated subsequently. Nuclear features of the cells relating to histologic grade and prognosis as described by Siegel et al.\(^\text{(17)}\) were observed in each case and correlated with the architectural pattern using Fischer’s exact test and statistical analysis was done by GraphPad.

**RESULTS**

In the current study a total of 201 CT guided lung FNA were performed in the mentioned period. Among them 86 cases (43%) were suspicious of adenocarcinoma on the basis of cellular features on smears. Those 86 cases were included in the study. Of them 21 were women and 65 were men. The age range at diagnosis was 30-81 years (mean 58 years).

Clear architectural as well as cellular evidence of adenocarcinoma \[1\] in the form of acini and papillae, flat 2D sheets and 3D cell balls were revealed in the cytology smears of 52 cases (62.6% of diagnosed ADC). Out of these smears, 10 cases showed large complex 3D clusters. CBs in these cases also showed solid sheets along with architectural evidence of ADC. Thirty four cases showed these large complex 3D clusters without presence of convincing ADC pattern in the smears \[2\]. Amongst them CB morphology showed acini, papillae and string of pearl either alone or in combination with solid sheets in 12 cases \[3\]. CB morphology confirmed adenocarcinoma in those cases. The remaining 22 cases did not show any evidence of ADC pattern even in cell block morphology. Mucin stain (D-PAS) done on these CBs showed positivity and predominance of positive cells \[4\] in 16 cases, thus confirming them as adenocarcinoma.

In the remaining 6 cases, mucin stain of CB sections showed either negativity or rare weak positivity. Only 3 of them showed positivity for Napsin A and depended solely on IHC for their confirmation as ADC \[5\]. Three cases showed negative result for Napsin A and were excluded. Two out of these 3 showed positivity for P63 and diagnosed as non-keratinizing squamous cell carcinoma. The other one was negative for squamous marker and was diagnosed as NSCC NOS. Thus, a total of 83 cases were finally diagnosed as ADC \[6\].

To sum up, among these total adenocarcinoma cases, 41 cases were ADC with solid pattern showing large complex 3D clusters in either smears \[7\] or solid sheets in CBs \[8\]. Of these 41 cases, 22 cases had expression of ADC patterns in CBs with (10 cases) or without (12 cases) the same patterns in the smears. CB morphology played vital role in diagnosis of ADC in these 12 cases. A total of 19 cases showed only large complex 3D clusters in smears and solid pattern in the CBs without showing any ADC pattern in the smears or CBs. Sixteen (19% of ADC) out of these 19 cases were diagnosed by mucin stain and the remaining 3 cases (3.6% of ADC) needed IHC for their diagnosis. CBs played a vital role as a platform for mucin stain and IHC in these 19 cases.

Majority of the cases of ADC showing non-solid patterns presented with various combinations of acini, papillae and string of pearl. Most frequent combination was that of acini and

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**Figure 1**: Composite image showing different patterns of tumor cells in FNAC smears: (a) Acini and 3D cell balls. (b) Pseudo papilla and true papilla with core. (c) Pseudo papillae with intracytoplasmic mucin blobs. (d) Monolayered 2D sheet with peripheral cells showing nuclei bulging outwards. (e) Closely spaced acini resembling cribriform pattern. (f) Complex 3D clusters. (a-c, e and f: MGG stain, 400X magnification; d: Papanicolaou stain, 400X magnification)

**Figure 2**: Composite image showing different patterns of tumor cells in Cell block sections: (a) Solid sheet with acinar pattern. (b) Papillae with signet ring cells. (c) Papillae. (d) Cribriform pattern. (e) String of pearl and acini. (a-e: H and E stain, 400X magnification)
Combination of acini, papillae and lepidic pattern was seen in 4 cases. Only 5 of them presented with single pattern (acini 2, papillae 3). Signet ring cells were identified in CBs of 22 cases of which 14 cases had only solid pattern in CB morphology [Figure 3d]. Thus, CB morphology reflected solid pattern with signet ring cells. Signet ring cells were also seen in one of the cases in which only papillary pattern was appreciated [Figure 2b]. Cribriform pattern [Figure 2d] was appreciated in CBs of 6 cases of which 3 cases showed solid pattern (solid with cribriform pattern). Corresponding FNAC smears also showed closely spaced small acini resembling cribriform pattern [Figure 1e]. Other distribution of signet ring cells and cribriform patterns with non-solid patterns are depicted in Table 2.

High nuclear grade (score 4 or 5) as described by Sigel et al. was observed in 39 out of 41 cases having solid pattern in CBs and large complex 3D clusters in FNA smears. This high nuclear grade was observed in only 7 cases out of 42 cases presented with non-solid patterns. Fisher exact test revealed significant correlation ($P < 0.0001$) of high grade nuclear features with cases having solid pattern in our study. Background necrosis was seen in 26 out of 41 cases having solid pattern and only in 5 cases out of 42 cases presented with non-solid pattern. Majority of the remaining 37 cases had a background showing extra cellular mucin.

**DISCUSSION**

Small biopsy or cytology specimen has quite reasonably become the most common targeted specimen for lung carcinoma cases.

![Figure 3: Composite image showing solid pattern of tumor cells in Cell block sections. (a and d: H and E stain, 400X magnification; b: D-PAS stain, 400X magnification; c: IHC for Napsin A, 400X magnification)](image-url)
Greater patient compliance, lesser complications and greater cost compliance has made cytology specimen very important in many centres. As per WHO 2015 recommendation, identifiable pattern present should be described in small biopsy or cytology specimens. This clearly signifies that cytology specimens having any pattern of arrangement reflecting any specific histology pattern should be recognised. The prognosis will be driven by predominant pattern or by presence of solid or micropapillary pattern.\(^5,6\) Although primary pattern cannot be assessed from the cytology specimen, presence of cytology features indicative of acinar, papillary and solid patterns were appreciated.

In the current study, 52 out of total 86 cases (60%) were diagnosed as adenocarcinoma of lung from FNAC smears alone on the basis of cytomorphology and ADC pattern. Cell block morphology played a complimentary role. In an additional 12 cases (14%), CB morphology helped in the diagnosis by representation of adenocarcinoma pattern which were not well appreciable in the smears. Therefore, in 64 out of total 86 cases (74%), the diagnosis of adenocarcinoma was made only on the basis of cytomorphology and ADC pattern. Nicholson et al. showed that a diagnosis of adenocarcinoma can be made on morphology alone in the biopsy or cytology specimens in 50-70% of the cases.\(^18\) The use of CB for appreciation of ADC pattern could be an explanation for better result in our study.

Mucin stain (D-PAS) aided the diagnosis in another 16 (19.3%) cases. Diagnosis of adenocarcinoma depended on IHC in only 3 out of 86 cases (3.5%). Judicious use of IHC and/or mucin stain (when available) is recommended for cases of non-small cell lung carcinoma that cannot be classified based on morphology alone so that necessary amount of material can be made available for molecular testing in case of limited specimen.\(^16,18,19\)

Rodriguez et al. have mentioned in their study that papillary tufts with central clearing and absence of definitive fibrovascular core can be found in cytology specimens representing papillary pattern but this can be difficult to distinguish from acini or lepidic pattern.\(^113\) Thirty two out of 83 ADC cases (38.6%) in which we had observed papillary pattern mostly had fibrovascular core either in the smear or CB. Effective chiselling along with sustainment of negative pressure during aspiration could be of help in getting tissue fragments in the form of mini biopsy and thus representing papillae with core in our cytology specimens. Complete acinar structure present in the smears and CBs in our study is indicative of acinar histologic pattern. ‘String of pearls’ in CBs in our study could be representative of either broken acini or lepidic histologic pattern. Occasional presence of outward nuclear bulge (hobnailing) and absent or mild pleomorphism could be reflective of lepidic pattern.

Many of the cases having acinar pattern showed presence of intracellular mucin blobs in smears or signet ring cells in CBs and extracellular mucin in the background. Some studies have shown that Alk rearranged adenocarcinomas apart from young age, non or light smoking history are characterized by acinar structures with mucin or signet ring cells.\(^4,20‑23\) Cytology features showing large complex 3D clusters in smears and large solid sheets in CBs are supposed to indicate the presence of histologic solid pattern. Rodriguez et al. in their study have found large 3D clusters in 5 out of 6 (83%) of ADC solid type. In another study by Rudomina et al., the presence of large clusters in smears was found to have predictive value of 39% for solid type ADC.\(^20\) Marked nuclear pleomorphism, nuclear contour irregularity, prominence of nucleoli and background necrosis were other features. Number of cases showing this pattern were 41 (49.4% of ADC), of which association with signet ring cells were seen in 14 cases. Different studies have shown that ROS1 rearranged adenocarcinoma is clinicopathologically characterized by solid growth with signet ring or cribriform morphology.\(^20\) Cribriform pattern in our study was appreciated in 6 cases whereas solid with cribriform pattern was found in only 3 cases. Appreciation of specific cytologic features may allow for better identification of prognostically adverse solid and cribriform patterns.\(^26‑28\)

The presence of micropapillary pattern to any extent is indicator of bad prognosis.\(^29\) Micropapillary as predominant pattern is relatively rare, and it is usually observed in combination with other patterns. We have observed small tight tufts of cells without stroma or fibrovascular core in 11 cases. However since any study describing the actual cytologic features with matched histology demonstrating single (pure) micropapillary pattern is lacking, we failed to recognize those structures as true micropapillae in our study. The non-availability of resection specimens owing to advanced stage of presentation is a potent obstacle to conduct this type of study with matched histology. Sub classification of ADC in cytology specimen is challenging and criteria remains to be developed. The current study simply reflects that morphologic pattern and significant cytomorphic appearance can be appreciated from adequately cellular FNAC smears and corresponding cell blocks of optimal quality. Meticulous examination to appreciate the actual cellular features and ADC pattern can be of great help in reaching at diagnosis of ADC. Thus, the need for special stain or IHC can be minimised and adequacy of material for molecular genetic analysis can be increased.

Appreciation of these findings can lead to scope of further study to find out the association of each molecular or genetic abnormality with different patterns in cytology specimens.

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Conflicts of interest

There are no conflicts of interest.

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