Primary lung cancer remains a leading cause of death for both men and women in the United States and most Western countries, with mortality rates exceeding the rates of breast, colon and prostate cancers combined. Only a minority of patients with lung cancer can be offered potentially curative treatment and only half of those will actually be cured. Clearly there is a need to reduce mortality and this will depend to a large extent on improved therapies and/or detection of early or preinvasive cancer.

The World Health Organization (WHO) recognizes three pre-invasive conditions which are thought to be precursors of malignant lung tumors: A) Squamous dysplasia as precursor of squamous cell carcinoma; B) Atypical adenomatous hyperplasia as precursor of adenocarcinoma; C) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia as a precursor of carcinoid tumors and related neuroendocrine carcinomas. This review focuses exclusively on atypical adenomatous hyperplasia.

First described in the 1930’s, atypical adenomatous hyperplasia (AAH) refers to a proliferative non-inflammatory lesion of the alveolar epithelium. Essential histopathologic features of AAH include small size (5.0 mm or less), focality and atypical cuboidal to low columnar alveolar epithelial cells lining the alveoli. Currently, AAH is regarded as a precursor lesion of pulmonary adenocarcinoma (AD) and particularly of its variant, the localized non-mucinous bronchioloalveolar carcinoma variant (BAC) and is therefore of much interest to both basic scientists and clinical investigators. As radiologists continue to enhance the resolution power of their diagnostic imaging techniques, a greater number of AAH lesions are likely to be identified leading to an even greater level of interest in this lesion.

**Frequency**

The frequency of AAH in the general population is not known. Miller et al examined 247 cases of surgically resected lung carcinomas and found 23 (9.3%) AAH lesions that were termed bronchoalveolar adenomas. AAH’s were identified in 67 (12%) of 582 surgically resected lung cancers in the series reported by Chapman and Kerr. Among the 582 lung cancers 224 (38%) were adenocarcinomas and in this subgroup AAH lesions were encountered in 52 (23%) of the 224 cases. AAH can be either single or multiple and is known to occur in association with carcinomas other than adenocarcinomas. One report documented as many as 42 AAH’s in a single surgically resected specimen. As indicated by Kerr the overall reported prevalence of AAH in surgically resected adenocarcinomas ranges from 12-35%. The prevalence of AAH is lower in large cell carcinoma and even lower in squamous cell carcinoma.
There is only limited data on the frequency of AAH in autopsy populations. In a study of 100 consecutive autopsies Sterner et al found only 2 cases of AAH. None of the 100 cases revealed any unsuspected or concurrent lung cancers.\(^7\)

**Clinical features**

There are no clinical signs or symptoms directly referable to AAH. The lesions are usually encountered as incidental findings radiographically or at gross inspection at the surgical pathology bench or, more often incidentally, upon microscopic examination of the lung.\(^3\)

**Radiological Imaging**

On high resolution CT, AAH appears as small nodular areas of pure “ground glass opacity” (GGO). These GGO’s appear as areas of increased opacification with distinct borders, not completely obscuring the underlying lung parenchyma, measuring 2-24mm in diameter, and typically not visualized on plain chest radiographs.\(^2,8-11\) Resection of GGOs has shown a range of pathology including benign disease in up to 30\%, AAH in 10-77\%, BAC in up to 50\% and invasive adenocarcinoma in 10-25\% of cases.\(^8,9,10,11,12\) In our lab, some of the GGO’s have been found to be granulomas and some others intrapulmonary lymph nodes and others yet small sized bronchioalveolar carcinomas (unpublished data).

**Cytology and Histopathology**

A diagnosis of AAH cannot be made on a cytology specimen. This is due in part of the generally small size of AAH and its peripheral location. To the naked eye, peripheral AAH lesions appear as grey tan white poorly defined nodules within close proximity to the pleura.\(^4,5\)

Microscopically, AAH’s appear as focal single or multiple proliferative lesions growing at the periphery of the lung. The basic histopathological feature of AAH is focal proliferation of alveolar cells spreading along the preexisting alveolar framework.\(^13-19\) The cells composing AAH are cuboidal to low columnar, apt to be mildly to moderately atypical with increased nuclear cytoplasmic ratio, often possessing hyperchromatic nuclei and prominent nucleoli. Rao et al. noted that the size of cells found in AAH was at least double the size of neighboring normal alveolar epithelial cells.\(^17\) Mitotic figures are rarely seen in AAH. Intercellular attachments are generally intact, with occasional empty looking spaces between the atypical cells. High cellularity, tufting and papillary structures are generally not seen in AAH.\(^18\) The pulmonary interstitium in the background may show some fibrosis but this is generally mild, without dense scar formation or significant chronic inflammation.\(^16\)
Grading

Much as been written in terms of grading AAH as either low grade or high grade AAH but the WHO does not recommend grading and we also tend not to engage in such grading. However, some authors do not conform, and continue to grade these lesions. Some actually recognize an intermediate grade and in fact some of the work cited / discussed below derives from studies that divide AAH into subcategories.

Diagnosis

The most recent communication from the WHO defines AAH as a focal lesion, often 0.5 cm or less in diameter, in which the involved alveoli and respiratory bronchioles are lined by monotonous slightly atypical cuboidal to low columnar epithelial cells with dense nuclear chromatin, a prominent nucleolus and scant cytoplasm.\(^2\)

Mori and associates have proposed a set of histopathologic changes, that if present, may aid in the diagnosis of AAH.\(^{18}\) These criteria are architectural as well as cytologic parameters and include focality, cuboidal to low columnar cells, dense nuclear chromatin, presence of nucleoli and high nuclear cytoplasmic ratio. Other features included thickened alveolar wall and fibrosis and empty looking spaces between atypical cells, increased cellularity and pleomorphism and high cellular density.\(^{20,21}\)

None of these suggested sets of histopathological criteria have been tested for reproducibility by practicing pathologists. Therefore, a consensus conference and/or creation of referral centers as suggested by Mori et al may help to accumulate useful data for analysis. For the moment, available data suggests that focality, small size (5 mm or less), well defined borders, lepidic spread, cuboidal shape and dense chromatin may be helpful and reproducible features that may facilitate the histopathologic recognition of AAH and its distinction from small sized bronchioloalveolar carcinoma.\(^{18-21}\)

Differential Diagnosis

AAH must be differentiated histopathologically from reactive alveolar epithelial hyperplasias resulting from exposure to drugs, viral infections, interstitial pneumonitis, diffuse alveolar damage, alterations due to circulatory disturbances, the so-called Lambertosis (bronchiolization of alveolar septae), alveolar cell hyperplasia occurring in adolescent patients following chemotherapy, nodular type II pneumocyte hyperplasia associated with tuberous sclerosis and AAH occurring in the setting of the Li-Fraumeni Syndrome.\(^{18,22-25}\) Distinction from these conditions usually does not pose a major problem if the clinical setting is correlated with the histopathological findings. Other distinctions, such as those between AAH and small-size BAC and AD are however considerably more difficult. In attempting to make these distinctions, the use of morphometry, flow cytometry, cytogenetics, and molecular studies, have contributed significantly to improve our understanding of AAH.
Regrettfully, while these studies are of much importance in determining the nature and pathogenesis of AAH, they have not, as of yet become readily available at the level of the surgical pathology bench. Accordingly, effort has been directed to the development of histologic criteria that may be of use to practicing surgical pathologists in making the diagnosis of AAH. Recent modified criteria for the staging of lung cancer formulated by the American Joint Committee for the staging of lung cancer has added a new sense of urgency to this issue, as a pathological diagnosis of adenocarcinoma (AD) of less than 3.0 cm in size with an associated AAH in the ipsilateral lobe may still be classified as a T1 tumor; while a 3.0 cm or less AD with a smaller associated AD in the same lobe will warrant an upgrade to a T4 classification, with significant therapeutic implications.

**Histogenesis**

The origin of AAH cells is still unknown but differentiation phenotypes derived from immunohistochemical and ultrastructural features suggest an alveolar origin. In particular, type II alveolar epithelial cells appear to be at the crossroad of inflammation, fibrogenesis and neoplasia and are likely to play a key role in the development of AAH. Surfactant apoprotein, and Clara cell specific protein are expressed in almost all AAH lesions.

Ultrastructurally, cytoplasmic lamellar bodies and nuclear branching microtubules, both typical of type II pneumocytes, and electron-dense Clara cell-type granules are found. AAH cells are likely derived from a progenitor cell with the potential for both type II pneumocyte and Clara cell differentiation.

**Morphometry and Cytofluorometry**

Various studies have measured AAH using morphometric methods. Mori et al measured mean nuclear area, total cellular area and other parameters and compared AAH to overt adenocarcinoma and were able to separate AAH from the Clara cell type of adenocarcinoma but not from Type II adenocarcinoma. The mean cell DNA content in AAH has been shown to be higher than in reactive pneumocyte hyperplasia, but lower than that found in small sized adenocarcinomas. Aneuploidy has been shown to be present in 77-85% of adenocarcinomas but also in 36-54% of AAH lesions.

**Immunohistochemistry**

AAH expresses surfactant apoproteins, carcinoembryonic antigen, matrix metallo-proteinases, thyroid transcription factor 1, E-cadherin, ß-catenin and CD44v6. The expression of oncogene and tumor suppressor gene products (p53, c-ErbB2, RB) support a neoplastic progression from AAH to BAC and invasive adenocarcinomas. In contrast to p53 mutations, p53 protein accumulation seems to occur early in the proposed sequence of events.
Somatic genetics and ploidy

Mutations of the K-ras gene, particularly at codon 12, are specific for peripheral lung adenocarcinomas, suggesting an alternative pathway of peripheral lung tumorigenesis. K-ras codon 12 mutations are reported in 15-39% of AAH lesions, and up to 42% of concurrent adenocarcinomas. One study found K-ras codon 12 mutations in 15% of AAH, 33% of “early” bronchioloalveolar carcinoma (BAC) and 24% of “advanced” BAC, suggesting that K-ras codon 12 mutation is a very early event in the development of peripheral adenocarcinoma.\textsuperscript{3,20,35,36,37}

Abnormalities of the p53 gene (17p), with impaired protein function, promote neoplastic transformation in affected cells. Many lung adenocarcinomas show missense mutations of the p53 gene with abnormal nuclear protein accumulation. LOH and mutations of the p53 gene are very rare in AAH compared with adenocarcinoma; however p53 protein overexpression is frequent in AAH.\textsuperscript{20} p53 mutation has been demonstrated with increasing frequency in the progression from AAH, through BAC to early invasive adenocarcinoma.\textsuperscript{3,18,20,38}

LOH allelic-specific losses at 3p and 9p loci have been detected in AAH.\textsuperscript{39} Some AAH lesions have shown LOH in 9q and both 17q\textsuperscript{39} and 17p LOH in the 3p and 9p loci probably occurs at a very early stage and may represent the earliest and crucial event in neoplastic transformation, with 17p events occurring later.\textsuperscript{3}

FISH studies of AAH have shown frequent aneuploidy of chromosome 7.\textsuperscript{40} The percentages of aneuploid cells and mean chromosome copy number increases from AAH to invasive adenocarcinomas, suggesting increasing polyploidy during malignant change.

Clonality

Studying DNA extracted for clonal analysis with an X-chromosome-linked polymorphic marker (the HUMARA marker) Niho et al,\textsuperscript{41} assessed the clonality status of seven females with AAH. A monoclonal pattern of HUMARA amplification was detected in all of the informative cases. Control cases with bronchiolar metaplasia were polyclonal.

Telomerase

Nakanishi et al studied human telomerase RNA expression and telomerase reverse transcriptase mRNA using in-situ hybridization in formalin-fixed paraffin-embedded AAH and localized non mucinous BAC. Expression of both was found in 27% of low grade AAH, around 75% of high grade AAH and 98% of BAC’s. These data support the neoplastic progression of low grade AAH through a higher grade lesion to localized non mucinous BAC.\textsuperscript{42}
Prognosis

Several studies of patients with surgically resected adenocarcinoma have compared post-operative survival in groups of patients with and without AAH. *None has showed any significant difference in outcome.* There is no indication for surgical or medical therapy in patients without cancer who are incidentally found to have AAH. But as noted below this point of view is not university accepted.\(^43,44\)

Takigawa et al showed a tendency for patients with AAH to have a surprising better survival; however, the difference was not significant. Other studies have failed to show any difference in survival between those with and without AAH. For many patients the outcome will be primarily determined by the cancer for which they had surgery.\(^3,43,44\)

Management

Some workers have proposed a conservative approach to the handling of AAH lesions. Briefly, this approach suggests that small AAH lesions, less than 0.5 cm without clinical or anatomical correlates and without compelling histopathology (“ie” atypical cuboidal to low columnar cells with dense chromatin, prominent nucleoli and scant cytoplasm) can be safely designated as AAH and be treated in a very conservative fashion. *Conversely,* small, 0.5 cm or more proliferative lesions with clinical, radiographic or anatomical correlates, and with compelling histology (as outlined above) can be classified and treated as bronchioloalveolar carcinoma. If available, specialized technologies such as morphometry, immunohistochemistry and molecular studies as cited above may be used to support histopathologic diagnoses.

Conceptual Problems

Travis and others have raised some concerns related to AAH.\(^45\)

- Recognizing AAH implies the existence of a non-atypical or a low grade variant or both, a debatable issue.
- As noted above, distinction from BAC, particularly its localized non mucinous variant is difficult.
- The implications for patients with AAH but no concurrent cancer are uncertain and much controversy exists in terms of management (see SUMMARY below).

Summary and some “points to take home”

Atypical adenomatous hyperplasia of the lung is a proliferative non inflammatory lesion of the alveolar epithelium defined by the WHO as a focal, single (but frequently multiple), often 0.5 cm or less in diameter lesion in which the involved alveoli and respiratory bronchioles are lined by slightly atypical cuboidal to low columnar epithelial cells with dense nuclear chromatin, prominent nucleolus and scant cytoplasm. The cells of AAH express SPA, CEA, MMP’s, TTF-1, CD44v6, E-cadherin, and \(\beta\) catenin. Ultrastructurally, features of alveolar origin can be seen. K-ras mutations occur in up to
39% of the cases and p53 protein overexpression is a common event. Some AAH lesions have shown LOH in 9q, 17q and 17p. Aneuploidy of chromosome 7 is also frequent.

These and other features not addressed in this brief review (such as altered cell proliferation indices) provide mounting evidence suggesting a role of AAH as a precursor lesion in the development of adenocarcinoma and supporting the following “take home” messages:

- AAH is a proliferative lung lesion derived from alveolar epithelium that is known to usually occur in association with invasive adenocarcinoma.
- AAH is a monoclonal lesion showing morphologic, morphometric, immunohistochemical, genetic and clonal features commensurate with neoplasia.
- The morphological progression of AAH is paralleled by progression in gene alteration and protein expression.
- AAH is similar to but distinct from localized non mucinous BAC, a lesion which most likely develops from AAH.
- To date, there is no objective data indicating a difference in outcome for patients with adenocarcinoma with or without AAH.
- A practical approach to the management of AAH suggests that lesions 0.5 cm or less without clinical correlates and without compelling histologic evidence of malignancy be regarded as AAH and be managed in a conservative fashion with close follow-up. Conversely, lesions with clinical or radiological correlates, with compelling histopathologic evidence of malignancy (regardless of size) can be regarded as carcinomas and be managed as such.
- For those rare AAH lesions which are unassociated with cancer, close follow up and no medical therapy is indicated. However, some authors have advocated not only close follow-up and immediate smoking cessation but also a possible chemopreventive treatment.

References


