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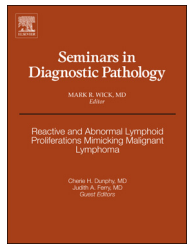

Adenosquamous carcinoma

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ABSTRACT

Adenosquamous carcinoma is an unusual and aggressive form of non-small cell lung carcinoma. Although extensively studied, there is persistent uncertainty with regard to its histogenesis and clinical and histopathologic features, related to the inherent heterogeneity of lung carcinoma. This review will attempt a reappraisal of the definition and diagnostic criteria and address problem areas and practical issues in the pathologic evaluation of this neoplasm.

Introduction

Adenosquamous carcinoma (ASC) is an unusual form of lung cancer, accounting for a small proportion of cases of non-small cell lung carcinoma (NSCLC). The WHO classification of lung tumors designates ASC as a distinct category, defining it as "a carcinoma showing components of both SCC and ADC with each comprising at least 10% of the tumor"[1] (Figs. 1A and 2A). The designation is not without problems, which particularly arise due to the inherent heterogeneity of non-small cell lung carcinomas. Adenocarcinomas (ADCs) often have solid areas with squamous features, and sometimes may contain foci of "squamoid" differentiation or benign squamous metaplasia adjacent to the tumor; conversely, squamous cell carcinoma (SCC) may show pseudoglandular features, or contain glandular foci representing benign epithelial inclusions (air spaces lined by hyperplastic type II pneumocytes or bronchiolar epithelium). Some SCCs may even contain focal stainable mucin, leading to further confusion in the histologic categorization of these tumors. There is also some uncertainty about the proportion of SCC and ADC components that are required to be present for a tumor to be regarded as ASC.[2–4] The criteria for diagnosis of adenosquamous carcinoma therefore may not be uniformly applied, leading to variation in the reported incidence and clinical and radiologic features. This review will attempt a reappraisal of the definition and diagnostic criteria, evaluate the literature, and address problem areas and practical issues in the pathologic evaluation of ASC.

Review of the literature

Non-small cell lung carcinomas are a heterogeneous family of tumors, with a significant proportion of tumors showing multiple lines of differentiation. This has been confirmed using electron microscopy and immunoperoxidase staining.[1,5–10] While it is generally agreed that ASC display areas that, by themselves, should be diagnosed as SCC or ADC by light microscopy, there is variable interpretation of what constitutes squamous and glandular differentiation. For squamous differentiation, the criteria have varied from invariably requiring the presence keratinization with squamous pearl formation and intercellular bridges, or a pattern of graded differentiation of tumor cells without requiring keratinization, to a much more flexible interpretation where simply a pavementing appearance is sufficient for squamous differentiation.[1,2,5] Similarly, for glandular differentiation, the presence of lepidic, acinar, tubular, or papillary arrangement patterns, with or without clear cell features, either singly or in combination, is required, although some authors believe that the presence of focal mucin (more than five droplets per high-power field) on histochemical stains is adequate to make a diagnosis of

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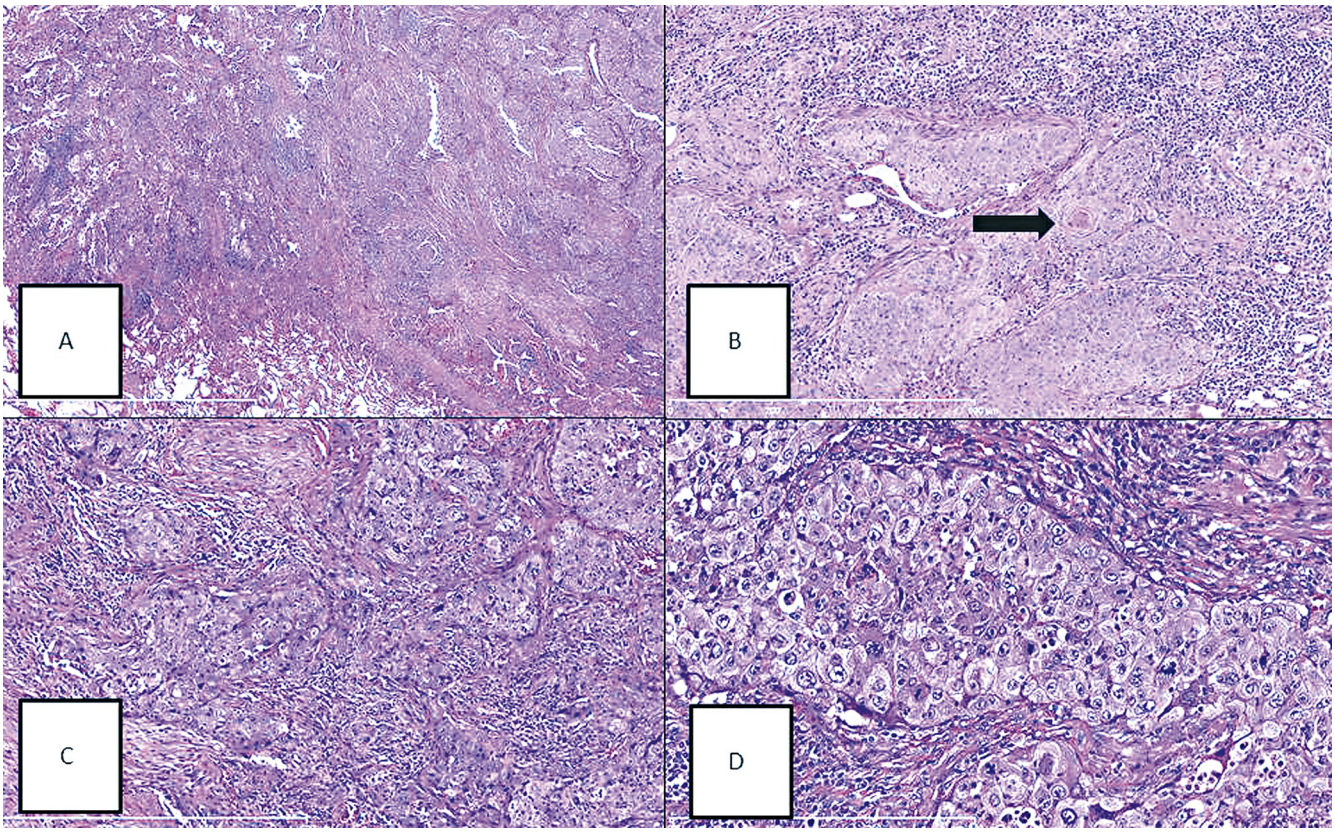

Fig. 1 – (A) Adenosquamous carcinoma. The tumor nodule shows roughly equal proportions of ADC (left) and SCC (right). (B) Well-differentiated squamous component with a squamous pearl (black arrow). (C) Moderately differentiated squamous component with masses of tumor cells with a polygonal appearance with eosinophilic cytoplasm. (D) Poorly differentiated squamous component with tumor cell groups with a "pavemented" appearance.

ADC.[1,2,5] The SCC and ADC components may be discrete and separate, or they may be closely intermingled with each other. One or the other components may be dominant, or they may be equal in proportion (Figs. 1A and 2A). Additionally, the degree of differentiation of the two components is not inter-dependent, with well, moderate, and poorly differentiated SCC (Fig. 1B–D) coexistent with ADC of variable differentiation (Fig. 2B–D). The reported incidence of ASC is variable in different series depending on diagnostic criteria; overall, it accounts for 0.4–4% of all lung cancers.[2,3,9,11–14] Several large series outlining the incidence and clinical/radiologic and histologic features of ASC have been reported. The clinical characteristics of ASC are variable and inconsistent, but predominance in men and an association with smoking have been reported.[2,3,14–17] Tumors can be centrally or peripherally located. By CT scan, centrally located tumors commonly show post-obstructive inflammatory changes, whereas peripheral tumors tend to present as ground-glass opacities.[16] Tumors with central location tend to be SCC predominant, whereas peripheral ASC tends to be ADC predominant.[8,13,16] In a retrospective study of 1125 cases of lung carcinoma, of which, 21 cases had been originally diagnosed as ASC, strict application of histologic diagnostic criteria yielded only seven cases of unequivocal ASC (0.6%).[3] Another large retrospective study of 873 cases of lung cancer showed a slightly higher incidence of ASC of 2.3%.[14] A major difference between the two series was the presence of cases diagnosed on small biopsies in the latter, whereas the former consisted almost exclusively (all but one case) of resection specimens. The diagnostic criteria in both of these series were similar. Takamori et al.[2] reported an incidence of 2.6% of ASC in a large series of 2160 resection specimens of lung carcinoma. Two other large series (103 and 127 cases respectively) using mainly biopsy material or cytology specimens estimated an occurrence of 8% of ASC of all lung carcinomas.[15,18] It is to be noted that none of these series relied on the application of ancillary studies, in particular immunohistochemistry, for diagnosis. With the increasing prevalence of immunohistochemistry, it is perhaps not unreasonable to believe ASC will be diagnosed more frequently.

While there is agreement on the presence of well-defined components of ADC and SCC, investigators have used different cutoffs for the proportion of each component that should be present. Takamori et al.[2] required at least 5% of the opposite component to be present. Fitzgibbons and Kern[3] made a diagnosis of ASC based on presence of at least 10% of the other component in each case. The 2004 WHO classification of lung tumors also stipulates that at least 10% of each component should be present in ASC.[1] According to the General Rules for Clinical and Pathological Record of Lung Cancer by the Japan Lung Cancer Society, ASC is defined as a tumor that is composed of at least 20% of each of SCC and ADC components.[4] In the largest reported series of ASC, three groups of tumors with $<20\%$, 20–80%, and $>80\%$ of ADC component, did not show any significant prognostic difference.[2]

The presence of discrete SCC and ADC components is essentially reflected in its immunophenotype. ADC markers,