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MINI-SYMPOSIUM: PATHOLOGY OF THE EXOCRINE PANCREAS

Pancreatic intra-epithelial neoplasia: current clinicopathological and molecular considerations

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Summary Based on clinical and molecular studies, pancreatic ductal carcinoma seems to follow a multistep progression sequence from low-grade dysplasia to high-grade dysplasia and eventually to invasive carcinoma; however, until recently, it was difficult to compare studies investigating dysplasia in pancreatic ducts due to the lack of consensus regarding the terminology and criteria for grading. In 2001, the term pancreatic intra-epithelial neoplasia (PanIN) was proposed for these lesions, and the criteria were established.

Accordingly, grading of PanINs follows a progressive increase of cytological and architectural atypia from PanIN/L-1A that are characterized by lack of cytological atypia to PanIN-1B characterized by increased crowding of cells with early papillary projections, to PanIN-2 characterized by similar architectural appearance with PanIN-1B but with mild to moderate nuclear atypia, and to PanIN-3 which resemble carcinoma, at a cytological level, demonstrating severe atypia, necrosis, tufting and mitotic activity.

Molecular evidence also supports that this progression is characterized by gradual accumulation of genetic alterations in cancer-associated genes that translates into inactivation of tumour suppressor genes and overexpression or aberrant activation of oncoproteins. These alterations can be categorized as 'early' such as k-ras mutation, HER-2/neu, prostate stem cell antigen, MUC5 and fascin overexpression; 'intermediate' such as p16 inactivation, MUC1 and cyclin D1 overexpression; and finally as 'late' such as p53 and deleted in pancreatic carcinoma locus 4 inactivation, BRCA2 mutation, and overexpression of ki-67, 14-3-3σ and mesothelin.

In terms of current pathology practice, it should be mentioned that PanINs-1 and -2 are common incidental findings and are generally not reported. If they are reported, this is followed by a note indicating their 'inconsequential' nature. PanIN-3, on the other hand, is strongly suspected to be a significant process that may require therapy. It is generally recommended that PanIN-3 should be documented in

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the surgical pathology report, especially in the absence of invasive carcinoma, keeping in mind that there are such cases on record that developed invasive carcinoma in follow-up.

Histopathologically, PanINs may be mimicked, on the one hand, by other incidental and significant ductal changes (reactive atypia, transitional/squamous metaplasia) and on the other hand by colonization/cancerization of native ducts by invasive carcinoma. It is also important to distinguish PanINs, both conceptually and diagnostically, from intraductal papillary mucinous neoplasias; the latter involve ducts >1 cm, typically form a cystic or nodular (intraductal papillary) mass and may have a different biology.

The recognition of PanIN is becoming increasingly important for cancer researchers and for clinical practice.

Terminology and historical perspective

Pancreatic ductal carcinoma ranks fifth as the cause of cancer-related deaths in the USA, and is therefore one of the most devastating malignancies. Annually, approximately 30 000 people are diagnosed with pancreatic cancer and their prognosis is very dismal with a 5-year survival rate not exceeding 4%.[1] Based on clinical and molecular studies, pancreatic ductal carcinoma seems to follow a multistep progression sequence from low-grade dysplasia to high-grade dysplasia and eventually to invasive carcinoma, that is similar to the adenoma–carcinoma sequence in colorectal carcinoma.[2]

One of the approaches to improve the ominous course of this neoplasm would be to effectively screen a high-risk population with a test that is capable of detecting precursor lesions.[3] This type of approach is successfully applied in colorectal neoplasia, where screening for adenomas in high-risk groups currently represents the standard of care. In pancreas, however, the study of precursor lesions and early cancer is more difficult than in other organs due to the relative inaccessibility of this organ to routine biopsy.

One of the first suggestions of precursor lesions for pancreatic carcinoma belongs to Sommers et al.[4] who noted an increase in pancreatic duct hyperplasia in patients with cancer compared with benign pancreata. Subsequent studies have identified hyperplastic or dysplastic lesions involving the small ducts of the pancreas, often found in association with invasive adenocarcinoma.[5–11] In a study of 227 cases of pancreatic carcinoma compared with 100 control autopsy cases without primary pancreatic cancer, Cubilla and Fitzgerald[5] noted that papillary hyperplastic lesions were more common in cancer cases than in non-neoplastic pancreata, and moreover, marked atypia and carcinoma in situ (CIS) were found to be exclusively associated with invasive carcinoma. These observations have triggered the assumption that these proliferative intraductal lesions may represent steps in the carcinogenetic evolution towards invasive carcinoma. Until recently, it was difficult to compare studies investigating dysplasia in pancreatic ducts due to the lack of consensus regarding the terminology and criteria for grading.[3] There were over 70 different terms, some of them redundant, from several different grading systems used to describe proliferative lesions involving pancreatic ducts.[12] In 2001, a consensus was reached that coined the term pancreatic intraepithelial neoplasia (PanIN) for these lesions,[12] as originally proposed by Klimstra and Longnecker[13] and Brat et al.[14]

Grading of PanIN

PanIN lesions are composed of ducts lined by cells with abundant intracellular mucin and variable cytological and architectural atypia manifested as nuclear enlargement, hyperchromasia, nuclear membrane irregularities, mitoses, nuclear crowding and pseudostratification, papillary of micropapillary formation and loss of polarity.[12] Grading of PanINs follows a progressive increase of cytological and architectural atypia from PanIN/L-1A that are characterized by lack of cytological atypia (they arguably could represent hyperplastic lesions) to PanIN-1B (ductal papillary hyperplasia) characterized by increased crowding of columnar cells with papillary projections, to PanIN-2 (ductal papillary hyperplasia with atypia) characterized by similar architectural appearance with PanIN-1B but with mild to moderate nuclear atypia, and to PanIN-3 which resemble carcinoma, at a cytological level, demonstrating severe atypia. Representative