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Dr. S.G. Deodhare

Former Professor of Pathology
Grant Medical College and Dean, J.J. Group of Hospitals, Mumbai

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The Weiss System for Evaluating Adrenocortical Neoplasms: 25 Years Later

Lau SK, Weiss LM.

The Weiss system is the standard protocol for the assessment and categorisation of adrenal cortical tumours, 20 plus years after the seminal publication. This review revisits the original criteria: high nuclear grade, >5/50 HPF mitoses, atypical mitoses, <25% clear cells, >1/3 diffuse architecture, necrosis and invasion (capsular, venous, sinusoidal), with three or more of these features corresponding to malignant behaviour. The modified Weiss criteria published in 2002 permitted greater reproducibility: mitoses >5/50 HPF, clear cells <25%, abnormal mitoses, necrosis, capsular invasion. Note that both paediatric tumours (>400 g, >10 cm, >15/20 mitoses) and oncocytic tumour (>10 cm, >200 g) require a slightly modified approach.

Hum Pathol 2009;40:757–68

Isolated Tumor Cells in Breast Cancer Sentinel Lymph Nodes: Displacement or Metastases? An Immunohistochemical Study

van Deurzen CH, de Bruin PC, Koelemij R, et al.

The origin, significance and progression of isolated tumour cells in breast cancer sentinel lymph nodes are uncertain. True lymph node metastases are often associated with aberrant protein expression by immunohistochemistry. This study explored proteins that are often overexpressed in breast cancer such as cyclin D1 and p53 to ascertain the malignant potential of these isolated tumour cells. Of 383 consecutive patients with primary invasive breast cancer and sentinel lymph node involvement, 40 had isolated tumour cells in the sentinel lymph nodes, of which 16 sentinel lymph nodes contained isolated tumour cells in newly cut sections that were available to study. Immunohistochemistry findings on the primary tumour and the isolated tumour cells in the sentinel lymph nodes were compared. Sentinel lymph node isolated tumour cells as a group showed significantly lower expression of cyclin D1 and p53 than micrometastases and macrometastases (controls). Cyclin D1 expression of the primary tumour and the corresponding sentinel lymph node metastases showed increased expression in micrometastases and macrometastases ($p=0.08$ and $p=0.0025$, respectively) compared with the corresponding primary tumour. In patients with sentinel lymph node isolated tumour cells, however, there was no substantial difference in cyclin D1 expression between the primary tumour and the corresponding isolated tumour cells. This supports the hypothesis that some of these cells may be displaced benign cells or are tumour cells with limited malignant potential compared with micrometastases and macrometastases.

Micrometastases or Isolated Tumor Cells and Outcome of Breast Cancer

DeBoer M, van Deurzen CH, van Dijck JA, et al.

The association of isolated tumor cells and micrometastases in regional lymph nodes with the clinical out-come of breast cancer is unclear. The authors identified all patients in the Netherlands who underwent a sentinel-node biopsy for breast cancer before 2006 and had breast cancer with favorable primary-tumor characteristics and isolated tumor cells or micrometastases in regional lymph nodes. Patients with node-negative disease were randomly selected during 2000 and 2001. The primary end point was disease-free survival. The study included 856 patients with node-negative disease who had not received systemic adjuvant therapy (node-negative, no-adjuvant-therapy cohort), 856 patients with isolated tumor cells or micrometastases who had not received systemic adjuvant therapy (node-positive, no-adjuvant-therapy cohort), and 995 patients with isolated tumor cells or micrometastases who had received such treatment (node-positive, adjuvant-therapy cohort). Median followup was 51 years. The adjusted hazard ratio for disease events among patients with isolated tumor cells who did not receive systemic therapy, as compared with women with node-negative disease, was 1.50 (95 percent confidence interval [CI], 1.15–1.94). Among patients with micrometastases, the adjusted hazard ratio was 1.56 (95 percent CI, 1.15–2.13). Among patients with isolated tumor cells or micrometastases, the adjusted hazard ratio was 0.57 (95 percent CI, 0.45–0.73) in the node-positive, adjuvant-therapy cohort as compared with the node-positive, no-adjuvant-therapy cohort. The authors concluded that isolated tumor cells or micrometastases in regional lymph nodes were associated with a reduced five-year rate of disease-free survival among women with favorable early stage breast cancer who did not receive adjuvant therapy. Disease-free survival was improved in patients with isolated tumor cells or micrometastases who received adjuvant therapy.

N Engl J Med. 2009;361:653–663

Venous Invasion by Elastica Van Gieson Stain and Tumor Budding to Predict Metastases in T1 Stage Colorectal Cancer

It may be difficult to evaluate pathologic predictors of metastases in T1 stage colorectal cancer using only hematoxylin-and-eosin staining. The authors conducted a study to clarify the role of pathologic predictors using immunohistochemical staining and Elastica van Gieson (EVG) staining. They studied 124 patients who underwent bowel resection for single T1 stage colorectal cancer from 1990 to 2004 in one institution. D2-40, EVG staining, and CAM5.2 were used to detect lymphatic invasion, venous invasion, and tumor budding, respectively. The authors evaluated these three factors separately based

on hematoxylin-and-eosin (H&E) staining. One pathologist reviewed histology. Lymph node metastases in the surgical specimen were the standard reference. Distant metastases were identified by periodic computed tomography for two years or more after surgery. A logistic regression model was applied to analyze risk factors for lymph node metastases. A Cox regression model was used for distant metastases. In predicting lymph node metastases, univariate analysis demonstrated significance for all predictors, except venous invasion by H&E staining. Multivariate analysis found that venous invasion by EVG and tumor budding by H&E showed significance as predictors. In predicting distant metastases, univariate analysis demonstrated significance for lymphatic in-vasion shown by D2-40, tumor budding shown by CAM5.2 and H&E, and lymph node metastases. Multivariate analysis showed only venous invasion by EVG stain as being significantly associated with distant metastases ($P=.001$). The authors concluded that evaluation of venous invasion by EVG staining is a useful pathologic predictor for metastases in T1 stage colorectal cancer.

Am J Surg Pathol. 2009;33(11): 1601–1607

Florid Reactive Lymphoid Hyperplasia of the Lower Female Genital Tract

Geyer JT, Ferry JA, Harris NL, et al.

Lymphoma-like lesions of the lower female genital tract are florid reactive inflammatory processes that primarily occur in women during their reproductive years. They are characterized by a dense lymphoid infiltrate with admixed large cells that is often suspicious for lymphoma. However, in contrast to lymphoma, they are superficial lesions that typically show surface erosion and a mixed lymphoid infiltrate and do not have evidence of a mass, deep invasion, or prominent sclerosis. In some cases, clonal rearrangement of the immunoglobulin heavy chain (IgH) gene potentially may lead to misdiagnosis. The authors conducted a study that examined the clinicopathologic features and outcomes of 12 patients with lymphoma-like lesions (nine in the cervix and three in the endometrium). The patients, who ranged in age from 18 to 54 years (median, 37 years), came to medical attention because of squamous dysplasia (eight patients), vaginal bleeding (three), or adnexal mass (one). One patient had an endocervical polyp, but otherwise none had a discrete mass. The specimens contained a dense, polymorphous inflammatory infiltrate commonly associated with mucosal erosion. Immunohistochemical studies showed a mixture of B and T cells without immunoglobulin light chain restriction. Four cases (all cervical) had a clonal IgH gene rearrangement by polymerase chain reaction. There was no evidence of lymphoma on staging or followup in any patient, including the four patients with clonal IgH rearrangement, after a mean followup of 3.5 years (range, four months to 13 years). The authors concluded that a clonal IgH rearrangement in this setting does not warrant a diagnosis of lymphoma. They recommended a search for infectious organisms with followup and rebiopsy at a later date. Careful correlation of clinical, histologic,

immunophenotypic, and genetic features is required to avoid misdiagnosis and inappropriate treatment. Routine microscopic findings and detailed clinical information are paramount in establishing the correct diagnosis.

Am J Surg Pathol. 2010;34(2):161–168

Histologic Assessment to Differentiate Multiple Lung Primary Nonsmall Cell Carcinomas from Metastases

Girard N, Deshpande C, Lau C, et al.

Lung adenocarcinoma is morphologically heterogeneous, with mixtures of acinar, papillary, bronchioloalveolar, and solid patterns in more than 80 percent of cases. In the case of synchronous or metachronous multiple nonsmall cell lung cancer (NSCLC), distinguishing intrapulmonary metastases from independent primary tumors is of great clinical importance as it influences staging and, potentially, therapeutic strategy. The authors undertook a study involving a cohort of 20 patients with 42 multiple NSCLC tumors (24 potential pair comparisons) that were annotated molecularly using genomic and mutational profiling to evaluate the value of comprehensive histologic assessment in this setting. Using the Martini-Melamed criteria, paired tumors were characterized as multiple primary NSCLCs in 21 cases and intrapulmonary metastases in three cases. Genomic and mutational data led to a diagnosis of multiple primaries in 14 cases and metastases in eight cases; two cases could not be assessed. This molecular characterization contradicted the Martini-Melamed diagnosis in seven of the 22 (32 percent) assessable comparisons. Adenocarcinoma was found in 32 of the 42 (76 percent) tumors. After review in a blinded fashion, semiquantitative comprehensive histologic assessment of paired tumors was different in 16 and similar in eight paired tumors. The authors found that comparing adenocarcinomas is a complex process that requires assessing not only percentages of the histologic subtypes, but also the recording of additional histologic details, such as cytologic features, patterns of stroma, necrosis, discrete nodularity versus miliary growth, and variants such as clear cell, signet ring, mucinous, and fetal patterns. The authors found too that paired squamous cell carcinomas could be compared based on histologic subtyping, as well as cytologic and stromal characteristics. Considering histologically different tumors as multiple primaries and similar tumors as metastases, comprehensive histologic sub-typing was consistent with the molecular characterization in 20 of the 22 (91 percent) pairs comparisons. The authors concluded that comprehensive histologic assessment is a powerful tool that shows promise in determining whether multiple lung adenocarcinomas or squamous cell carcinomas are metastatic or multiple primaries. This has great clinical implications for staging and therapeutic management of lung cancer patients with multiple tumors.

Am J Surg Pathol. 2009;33(12):1752–1764