Non-mycosis fungoides primary cutaneous T-cell lymphomas have a more favorable outcome than secondary cutaneous T-cell lymphomas; these lymphomas can be separated into indolent and aggressive groups.

**Background:** Non-mycosis fungoides (non-MF) primary cutaneous T-cell lymphomas (PCTCL) represent a heterogeneous group with variable clinical presentation, histology, immunophenotype, and prognosis. These are very rare lymphomas, which has made classification and study difficult. The current classification is a compilation of the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classifications.

**Objective:** To evaluate non-MF PCTCL in terms of the classification system, comparison with the European literature, and grouping based on indolent and aggressive clinical behavior.

**Methods:** Skin biopsies diagnosed as lymphoma were identified from the Cleveland Clinic pathology archives. All cases were stained and evaluated for T-cell receptor (TCR) gamma gene rearrangements. Clinical follow-up was obtained when possible, and overall survival was evaluated. Based on the results, the cases were classified according to the WHO-EORTC classification.

**Results:** In total, 44 cases were identified with a mean age range at diagnosis of 52 to 65 years. Most subgroups had a male predominance. Ten cases of secondary T-cell lymphoma secondarily involving the skin were also identified. The authors discussed each entity, and only a brief summary will be described here with a more extensive review discussed in the audio portion. The studied entities include: primary cutaneous anaplastic large cell lymphoma (PC-ALCL), subcutaneous panniculitis-like T-cell lymphoma (SPTCL), cutaneous gamma/delta T-cell lymphoma (CGD-PTL), primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma (AECD8), primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (CTLCD4), unspecified, primary cutaneous peripheral T-cell lymphoma (PC-PTCL, unspecified, and secondary CTCL. Non-MF PCTCL tended to have a longer median overall survival (OS) (approximately, 14 years) compared with SCTCL (2.5 years). PC-ALCL had the longest median OS of the entities with a large enough sample size (14 years). Both PC and SC-PTCLs had short OS. WHO-EORTC non-MF CTCL entities were able to be statistically significantly divided into 2 groups based on indolent and aggressive behavior.

**Conclusions:** The case series described correlates well with the current WHO-EORTC classification. PC-ALCL represents the most common distinct entity. Currently, the entities can be divided into clinically indolent and aggressive groups.

**Reviewer's Comments:** This is a challenging and evolving topic, with much of the knowledge coming from Europe. This is the first North American series that supports the previous findings and current classification system. (Reviewer-William A. Kanner, MD).

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Keywords: T-Cell Lymphoma, Skin, WHO-EORTC

Print Tag: Refer to original journal article
Can HPV Testing Triage Older Women With Pap Test Interpretation of LSIL?

Women ≥30 Years of Age With Low Grade Squamous Intraepithelial Lesion (LSIL) Have Low Positivity Rates When Cotested for High-Risk Human Papillomavirus: Should We Reconsider HPV Triage for LSIL in Older Women?

Thrall MJ, Smith DA, Mody DR:

Diagn Cytopathol 2010; 38 (June): 407-412

Women ≥30 years of age with a Pap test interpretation of low-grade squamous intraepithelial lesions are less likely to be positive for high-risk human papillomavirus than was found in the ASCUS/LSIL Triage Study trial.

Background: The ASCUS/LSIL triage study (ALTS) trial demonstrated that the high prevalence of high-risk human papillomavirus (HR-HPV) in low-grade squamous intraepithelial lesions (LSIL) (>80%) results in reflex testing for LSIL not being cost effective. However, the ALTS trial was predominantly composed of younger women who were at higher risk of HPV infection than the general population. With the advent of HPV cotesting for women ≥30, the value of HR-HPV testing in older women with LSIL is being re-examined.

Methods: Over a 2-year period, women ≥30 years old with a Pap test interpretation of LSIL were included. This study population represented a private practice population; high-risk populations were excluded. Any HR-HPV test results and follow-up biopsy results on these women were recorded. HR-HPV testing was performed with the Hybrid Capture II method. In the case of women with multiple biopsies, the biopsy with the greatest degree of dysplasia (CIN 2 or worse) was used for statistical analysis.

Results: 735 women ≥30 had a Pap test interpreted as LSIL during the study period. A total of 254 women (35%) had HR-HPV testing performed and 299 (41%) had cervical biopsies; 107 women (15%) had both HR-HPV testing and a follow-up biopsy. Of the women who underwent HR-HPV co-testing, 63% were positive. Women who tested positive for HR-HPV were significantly more likely to have a follow-up biopsy (55% vs. 25%). High-grade dysplasia was identified on biopsy in 23 women (11%), of whom 12 had HR-HPV co-testing. Of the subgroup of women with both HR-HPV testing and follow-up biopsy, a high-grade lesion was found in 14% (11/79) of women with a positive HR-HPV test compared to 4% (1/28) of women with a negative HR-HPV test. This difference was not statistically significant due to the small sample size.

Conclusions: Women ≥30 years of age with a Pap test interpretation of LSIL are less likely to be positive for HR-HPV than was found in the ALTS trial. There is a trend to find high-grade lesions more frequently in this population of women who are HR-HPV positive. Colposcopy triage may be justified in this population.

Reviewer's Comments: The most surprising result from this study is the very low rate of colposcopic follow-up and biopsy in women >30 years of age with a Pap test interpretation of LSIL. The fact that significantly more women had biopsies if they were HR-HPV positive suggests that the clinicians are already using HPV testing as an LSIL triage for colposcopy in older women. Whether this is justified is still uncertain. (Reviewer-Deborah J. Chute, MD).

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Keywords: Low-Grade Squamous Intraepithelial Lesions, HPV, Pap Test, Cervical Intraepithelial Neoplasia

Print Tag: Refer to original journal article
Glypican-3 May Help You Diagnose Yolk Sac Tumors

Glypican 3 Has a Higher Sensitivity Than Alpha-Fetoprotein for Testicular and Ovarian Yolk Sac Tumour: Immunohistochemical Investigation With Analysis of Histological Growth Patterns.

Zynger DL, McCallum JC, et al:

Histopathology 2010; 56 (May): 750-757

Glypican 3 reportedly shows higher sensitivity for detecting the various patterns of yolk sac tumor compared with α-fetoprotein.

**Background:** Glypican 3 (GPC3) is a heparin sulphate proteoglycan that is thought to play a role in regulating cell growth and differentiation. Recently, it has been shown that GPC3 mRNA is highly overexpressed in yolk sac tumor (YST) compared with other germ cell tumor (GCT) subtypes. Later studies have since reported GPC3 expression by immunohistochemistry in both gonadal and extragonadal YST.

**Objectives:** To compare the sensitivity of GPC3 with α-fetoprotein (AFP) for yolk sac tumors and to determine the expression characteristics of GPC3 among YST growth patterns.

**Methods:** 39 cases of formalin-fixed paraffin-embedded gonadal GCTs were selected for the study. The cases included 30 primary testicular GCTs, 5 primary ovarian GCTs, and 4 cases of metastatic GCT involving lymph nodes. Of the 39 cases, 27 were mixed GCTs and 12 were pure YSTs. Patterns of YST, listed in descending order of frequency, included microcystic, macrocystic, solid, glandular-alveolar, endodermal sinus, ployvesicular vitelline, enteric, and micropapillary. Immunohistochemical staining for GPC3 and AFP was then performed on a representative section from each case. A semiquantitative score reflecting the percentage of reactive tumor cells was then applied as follows: negative (0; <5%), focally positive (1+; 5% to 10%), positive (2+; 11% to 50%), and diffusely positive (3+; >50%). The intensity of staining was also recorded using a scale of 0 to 3, and a mean intensity value was calculated for each case.

**Results:** All cases showed GPC3 expression; 5% showed 1+ reactivity, 8% showed 2+ reactivity, and 87% showed 3+ reactivity. Cases also showed strong intensity of staining, with a mean intensity score of 2.9. A majority of cases expressed AFP (58%), but the degree of immunoreactivity was lower compared to GPC3: 42% showed 0 reactivity, 33% showed 1+ reactivity, and 25% showed 2+ reactivity. The mean intensity of AFP staining was also lower (1.0). With GPC3, >75% of growth patterns showed either 2+ or 3+ reactivity.

**Conclusions:** GPC3 is expressed in the major patterns of YST and appears more sensitive for YST compared to AFP. GPC3 also shows an increased staining intensity profile compared to AFP, which further supports its use as an immunohistochemical marker for YST.

**Reviewer's Comments:** It is interesting that GPC3 serum testing is also now available as a commercial assay for the identification and monitoring of hepatocellular carcinoma (HCC). The serum assay has also been shown to have greater sensitivity and specificity than AFP for HCC detection. (Reviewer-T. David Bourne, MD).

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Keywords: Yolk Sac Tumors, Detection, Glypican 3, α-Fetoprotein

Print Tag: Refer to original journal article
**Follicular-Patterned, Encapsulated Thyroid Nodules Are Rarely Fatal**

*Encapsulated Well-Differentiated Follicular-Patterned Thyroid Carcinomas Do Not Play a Significant Role in the Fatality Rates From Thyroid Carcinoma.*

Piana S, Frasoldati A, et al:

*Am J Surg Pathol* 2010; 34 (June): 868-872

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Encapsulated, follicular-patterned malignancies of the thyroid gland are unlikely to lead to the patient’s death.

**Background:** Follicular-patterned and encapsulated lesions of the thyroid account for a sizable proportion of what now is designated as carcinoma of the thyroid. These tumors include minimally invasive follicular carcinomas as well as encapsulated follicular variants of papillary carcinoma. In addition, some include tumors with equivocal features. Within these categories, vascular invasion appears to be the most predictive feature for metastasis. The data regarding the behavior of these tumors, although not typically prospective in nature, have shown that those tumors without vascular invasion behave in a very benign fashion. Some have even termed such tumors “nonthreatening.”

**Objective:** To review a series of lethal thyroid malignancies with particular attention to the original histologic features.

**Methods:** All thyroid cancers diagnosed at a single institution over a >25-year period were reviewed. Tumors were classified through review by 4 pathologists. At least 5 years of follow-up were available for almost all cases. Cases were reviewed again if it was determined that the patient had died of thyroid malignancy.

**Results:** 1,039 cases of thyroid malignancy were identified. Of these, 102 were diagnosed as encapsulated, follicular-patterned malignancies. Of the 1009 cases with follow-up, it was determined that 67 patients died of thyroid malignancy (37 women and 30 men). The mean age of those who died of thyroid cancer was 71 years (range, 22 to 91 years). All but 12 patients had undergone complete thyroidectomy. Of the 67 fatal cases, there were 29 papillary carcinomas, 6 medullary carcinomas, 17 anaplastic carcinomas, 9 poorly differentiated carcinomas, 2 Hürthle cell carcinomas, 3 widely invasive follicular carcinomas, and 1 mucoepidermoid carcinoma. Notably, none of the 67 fatal cases were follicular-patterned, encapsulated thyroid malignancies. Over all types of papillary carcinoma, only 3% caused the death of the patient. Thirteen percent of medullary carcinomas, 74% of anaplastic carcinomas, 43% of poorly differentiated thyroid carcinomas, 10% of Hürthle cell carcinomas, and 60% of widely invasive follicular carcinomas caused the death of their patients.

**Conclusions:** Follicular-patterned, encapsulated malignancies of the thyroid gland are indolent lesions that do not lead to the death of the patient.

**Reviewer’s Comments:** There is often much consternation regarding the assessment of individual thyroid nodules that are follicular-patterned and encapsulated. It is heartening to know that although therapy may differ depending on diagnoses, the lesions appear rarely, if ever, to lead to the death of the patient. (Reviewer: Edward B. Stelow, MD).

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Keywords: Papillary Carcinoma, Follicular Carcinoma, Mortality

Print Tag: Refer to original journal article
DLBCL Associated With Chronic Inflammation Can Occur in Variety of Locations

Diffuse Large B-Cell Lymphoma Associated With Chronic Inflammation as an Incidental Finding and New Clinical Scenarios.

Loong F, Chan ACL, et al:

Mod Pathol 2010; 23 (April): 493-501

Diffuse large B-cell lymphomas associated with chronic inflammation can occur in many settings other than effusions and seem to be consistently positive for Epstein-Barre virus.

Background: Diffuse large B-cell lymphomas (DLBCLs) arising in chronic inflammatory conditions are most frequently described in body cavities such as the pleural space (effusion-associated). These are characteristically positive for Epstein-Barr virus (EBV), and a proposed etiology is development from a nonautoimmune chronic inflammatory stimulus.

Objective: To describe incidentally detected DLBCL arising in association with chronic inflammation.

Methods: 4 cases were collected from 3 hospitals and were submitted for immunohistochemical staining for a variety of markers and molecular studies for EBV, kappa and lambda, and immunoglobulin gene rearrangement in 2 cases.

Results: The 4 patients ranged in age from 29 to 88 years. Each presented with a surgical condition, including a splenic cyst, chronic hydrocele (18 years), left atrial mass, and knee replacement re-do (32 years). The spleen contained an 18-cm cyst with a fibrous and calcified wall with patchy inflammation. Small aggregates (<1.5 mm) of atypical large lymphoid cells were found within the inner fibrous zone or necrotic material. The residual splenic parenchyma appeared unremarkable. The testicle was atrophic, with a 10.5-cm abscess cavity and a dense fibrous pseudocapsule with central necrotic debris and mixed acute and chronic inflammation. Clusters of atypical large cells were found within the central necrotic debris. In the 6.5-cm atrial tumor, typical features of a myxoma were noted with the addition of multiple tiny aggregates (<1 mm) of large lymphoid cells. In the knee replacement re-do, the wear debris of the joint showed necrotic material within hyalinized fibrous tissue and histiocytes with several small clusters of atypical large cells. The cells had irregularly folded or oval nuclei, occasional binucleated forms, distinct nucleoli, and a moderate amount of cytoplasm. Some were degenerated or necrotic appearing. They were CD20, CD79a, and PAX5 positive. All were nongerminat center type (CD10−, BCL6+/−, MUM-1+), highly proliferative (70% to 100% Ki-67 index), and positive for EBV latent membrane protein 1, EBV nuclear antigen 2, and EBV-encoded early small nuclear RNA on in situ hybridization (ISH). Cases 1 and 3 were positive for kappa ISH, but 2 and 4 did not express either. Cases 3 and 4 were positive for gene rearrangements by polymerase chain reaction.

Conclusions: Long-standing chronic inflammation in various enclosed spaces may provide a local immunodeficiency that allows for the development of a DLBCL, which is characteristically associated with EBV.

Reviewer's Comments: In contrast to the prototypical effusion-associated lesion, these had no tumor mass but were only noted to have small clusters of cells. (Reviewer-Mary T. Galgano, MD).

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Keywords: Diffuse Large B-Cell Lymphoma, Chronic Inflammation, EBV Infection

Print Tag: Refer to original journal article
High expression of mucin 4 is a predictor of poor survival in patients with colorectal carcinoma, particularly for patients with early stage disease.

**Background:** Mucin 4 (MUC4) is a transmembrane mucin that has been identified in a variety of normal and neoplastic tissues. MUC4 expression has been associated with reduced survival in patients with lung and pancreatic adenocarcinoma.

**Objective:** To evaluate the prognostic significance of MUC4 expression in colorectal carcinoma (CRC).

**Participants/Methods:** Patients who underwent surgical resection for CRC and had sufficient material available for study were included. Patients were excluded if there was surgical margin involvement, multiple primary tumors, a history of hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis, a personal history of CRC, or adjuvant therapy. The surgical pathology slides from each case were reviewed by 3 pathologists to determine tumor grade and stage. Immunohistochemical staining was performed on each case with antibodies against MUC4. A semiquantitative immunostaining score (ISS) was calculated for the tumor cells in each case; the percentage of cells at each staining intensity was multiplied by the intensity value (0 to 4) and added together to obtain a score between 0 and 4. Cases with an ISS ≥2.0 (>75% tumor cells with moderate expression) was considered high MUC4 expression. Patient clinical and follow-up information was obtained from the medical record.

**Results:** 132 patients met the inclusion and exclusion criteria. At the time of last follow-up, 46% of the patients had died of disease. In all cases, the normal colonic epithelium demonstrated moderate cytoplasmic staining, accentuated in the lower portion of the crypts. High expression of MUC4 was present in 25% of tumors, low expression was present in 69%, and MUC4 expression was absent in 6% of tumors. High expression of MUC4 was significantly associated with shortened disease-specific survival; in addition, patients with high MUC4 expression were 2.07 times more likely to die of CRC. In the subset of patients with early CRC (stages I and II), high MUC4 expression was also associated with significantly shorter disease-specific survival, and these patients were 3.77 times more likely to die of CRC. These associations remained statistically significant on multivariate analysis.

**Conclusions:** High expression of MUC4 is a predictor of poor survival in CRC, particularly for patients with early stage disease.

**Reviewer’s Comments:** Because MUC4 expression is present in normal colon, this stain is not useful as a diagnostic marker of malignancy. However, this normal expression may be helpful. While complicated ISS scores are useful for research purposes, they are impractical in the clinical setting. It appears that the level of normal expression is very close to the ISS 2.0 marker used in this study, and if MUC4 becomes a clinical tool, comparison with normal expression would be the easiest practical application. (Reviewer-Stacey E. Mills, MD).

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Keywords: Mucin 4, Colorectal Adenocarcinomas, Early Stage, Prognosis, Survival

Print Tag: Refer to original journal article
Blastic plasmacytoid dendritic cell neoplasm is an aggressive hematological disorder with morphologic and phenotypic variability.

**Background:** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare neoplasm that has been previously referred to as CD4+/CD56+ hematodermic neoplasm. BPDCN, as defined in the 2008 World Health Organization classification, is a neoplasm derived from precursors of plasmacytoid dendritic cells with a high incidence of cutaneous involvement, a propensity for leukemic dissemination, and commonly, an aggressive clinical course with a poor prognosis. Patients usually come to attention via the cutaneous manifestations, thus skin biopsies are critical to the diagnosis. On biopsy, the classical histology includes a monomorphic infiltrate of medium-sized blastoid cells that do not involve the epidermis and stain with CD4, CD56, CD123, and TCL-1.

**Objective:** To better characterize the clinicopathologic characteristics of the disease and the morphologic and phenotypic variants.

**Methods:** Cases were retrieved, reviewed, and included if consistent with the diagnosis of BPDCN. In addition to the histological examination, immunohistochemistry (which a large panel) and molecular analysis for immunoglobulin heavy chain genes (IgH) and T-cell receptor (TCR) genes was completed.

**Results:** 29 of the 33 patients were males, with a mean age of 67 years at diagnosis. More than half the patients presented with generalized skin lesions, but the remaining patients presented with either solitary lesions or lesions localized to a single body area. In most patients, the skin lesions were brown to violaceous infiltrated patches, plaques, or tumors. In 20 patients, complete staging was negative, while of the remaining patients with follow-up, 9 had extracutaneous manifestations. At 12 and 24 months, disease-specific survival rates were 60% and 51%, respectively, in patients with follow-up. Most cases presented with a nodular/diffuse infiltrate involving the entire dermis and often extending into the subcutaneous tissues. Although a “grenz zone” was present in the vast majority of cases, there were rare cases with either epithelial involvement or angiocentricity. The majority of cases presented with a pleomorphic infiltrate with admixed blastoid cells, some showing a centrocyte-like appearance. By immunohistochemistry, almost one-third of the cases lacked staining with 1 or 2 of the classic aforementioned stains, but no cases lacked all 4 markers. Other markers that stained cases included CD68 (usually scattered cells), terminal deoxynucleotidyl transferase, Bcl-2, Bcl-6, MUM-1, and FOX-P1. All tested cases were negative for both IgH and TCR gene rearrangements.

**Conclusions:** There is clinical heterogeneity, as some patients have solitary or flat lesions. Even patients with negative staging should be treated aggressively. The morphology is also variable and may be quite different from the classical description.

**Reviewer's Comments:** Although BPDCN is a rare lesion, this is probably the most comprehensive study on the topic, which is still being elucidated. The authors demonstrate that there is still significant clinicopathologic heterogeneity in BPDCN, and as of yet, there is no standard treatment algorithm. (Reviewer-William A. Kanner, MD).

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Keywords: Blastic Plasmacytoid Dendritic Cell Neoplasm, CD4+/CD56+ Hematodermic Neoplasm

Print Tag: Refer to original journal article
LVI Is Independent Predictor of Poor Prognosis

Is It Useful to Detect Lymphovascular Invasion in Lymph Node-Positive Patients With Primary Operable Breast Cancer?

Ragage F, Debled M, et al:

Cancer 2010; 116 (July 1): 3093-3101

Lymphovascular space invasion is an independent predictor of poor prognosis, even in patients with lymph node-positive breast cancer.

**Background:** Whether to use adjuvant chemotherapy in patients with early stage breast cancer is an important decision. This decision is still largely based on 5 prognostic factors: lymph node status; age; tumor size; estrogen receptor status; and histological grade. The prognostic value of lymphovascular space invasion (LVI) is well recognized in lymph node-negative patients, but there are limited and conflicting data about its significance in lymph node-positive patients.

**Objective:** To report the longest term research to date evaluating the utility of LVI in patients with lymph node-positive breast cancer.

**Participants/Methods:** Patients with primary, operable lymph node-positive breast cancer were prospectively entered into a research database. Clinical data, including treatment modalities used, age, and menopausal status, were recorded. All patients underwent either modified radical mastectomy or local tumor resection with radiotherapy, along with axillary node dissection. Adjuvant therapy with chemotherapy or hormone therapy was decided according to clinical variables. For each case, ≥3 blocks of tumor were examined by H&E. Tumor characteristics, including size, mitotic count, histologic grade, and lymph node status, were recorded. LVI was defined as carcinoma cells present with a definitively endothelial-lined space at a distance from the main tumor mass (preferably with intervening normal breast tissue). Equivocal cases were recorded as negative. Overall survival (OS) and metastasis-free survival (MFS) were calculated.

**Results:** 374 patients had sufficient clinical and pathologic data for inclusion in the study. The median follow-up interval was 150 months (12.5 years); 143 patients (38%) developed distant metastasis, and 115 (31%) died of disease. LVI was found in 171 patients (46%). LVI was significantly associated with younger age (≤40 years), high tumor grade, and negative estrogen receptor status. There was no correlation with tumor size or number of involved lymph nodes. Patients with LVI more frequently received adjuvant chemotherapy than patients without LVI. At 10 years, both the MFS and OS were shorter in patients with LVI (56% vs 74% for MFS and 58% vs 76% for OS). By multivariate analysis, LVI was an independent predictor of distant recurrence. LVI was also an independent predictor of poor outcome in the HER-2-negative and hormone receptor-positive subgroups of patients.

**Conclusions:** LVI is an independent predictor of poor prognosis, even in patients with lymph node-positive breast cancer.

**Reviewer's Comments:** Contrary to many expectations, this well-designed study demonstrates that LVI as assessed by H&E evaluation remains an important predictor in node-positive breast cancer. Some of the conflicting data from other studies may be due to shorter follow-up time or less strict definitions of LVI. Whether occult LVI detected by immunohistochemistry (endothelial markers or D2-40) will have the same prognostic impact remains to be studied. (Reviewer-Deborah J. Chute, MD).

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Keywords: Breast Cancer, Prognosis, Lymphovascular Invasion, Lymph Node Positive

Print Tag: Refer to original journal article
Measuring the urine concentrations of both aquaporin-1 and adipophilin may be a good way to screen patients for selected renal malignancies.

**Background:** As with many malignancies, early detection and treatment of renal cancer has substantial benefits for the patient. These include potentially longer overall survival, less invasive treatment modalities, and the potential for partial nephrectomy, which has the benefit of improved renal function. Thus, the benefit of identifying biomarkers for the most common renal cancers is significant. Protein expression analyses have shown that aquaporin-1 (AQP1) and adipophilin (ADFP) are overexpressed in various renal cancers, including clear cell renal cell carcinoma. AQP1 is a water channel protein located in the apical membrane of the proximal tubule, whereas ADFP is a lipid-droplet associated protein found in cells with clear cytoplasm as well as in macrophages. **Objectives:** To test the hypothesis that increased tumor expression of proteins such as ADFP and AQP1 in patients with renal cancer would be associated with increased urinary excretion of these same proteins. **Methods:** Pre- and postnephrectomy urine samples were collected from 42 patients with incidentally discovered renal masses by imaging, all of which carried a presumptive preoperative diagnosis of renal cancer. Control patients included individuals who underwent nonrenal surgery as well as healthy volunteers. Western blot analysis was used to determine AQP1 and ADFP concentrations in the urine. **Results:** In patients with a tissue diagnosis of clear cell or papillary renal cell carcinoma, the mean pre-excision urine concentrations of both AQP1 and ADFP were significantly higher than in patients with renal cancers of nonproximal tubular origin, in patients who underwent nonrenal surgery, and in healthy volunteers. Furthermore, the concentrations of AQP1 and ADFP in urine decreased by at least 88% after patients underwent nephrectomy. Additional findings included a linear correlation between tumor size and pre-excision AQP1 or ADFP concentrations. **Conclusions:** Both urinary AQP1 and ADFP concentrations appear to be sensitive and specific markers of common renal cancers, and measuring their protein concentrations in the urine may prove to be a valid and useful way to screen for selected renal tumors. **Reviewer's Comments:** The aims and results of this study reinforce the general thrust of many translational research projects to identify useful biomarkers as tools for cancer screening. The use of cell-free plasma DNA or other nucleic acid test modality may eventually provide even greater sensitivity and specificity in the setting of renal carcinoma screening compared with protein concentration assays. (Reviewer-T. David Bourne, MD).
The incidental presence of atypical lobular carcinoma in situ on a breast core biopsy by itself does not warrant follow-up excision.

**Background:** Breast biopsy to determine follow-up for clinically or radiographically suspicious breast lesions is the standard of care. The follow-up recommendations for the diagnosis of lobular neoplasia on core biopsy, especially atypical lobular hyperplasia (ALH), remain controversial. These diagnoses typically do not cause mass lesions or radiographic abnormalities. Both lesions are typically considered risk factors for breast cancer but not definitive precursors.

**Objective:** To specifically investigate excision and follow-up data for incidentally discovered ALH and lobular carcinoma in situ (LCIS) on biopsy.

**Methods:** All breast core biopsies diagnosed as ALH or LCIS with follow-up excisional biopsies seen at a single institution over a 10-year period were reviewed. The numbers of ALH foci were counted (a focus was 1 to 4 adjacent lobular units affected by ALH). ALH was defined as monotonous proliferations of discohesive cells. If acini were filled and there was an expansion of at least half the lobular unit, cases were diagnosed as LCIS. Cases with discordant calcifications or clinical mass lesions were excluded as it was believed that the core biopsy results did not explain the pretest abnormality.

**Results:** Of the >10,000 breast core biopsies, 117 showed ALH only without discordant calcification or mass lesion history. Fifty-six of these had paired excisional biopsies. Twenty-six showed only LCIS. Forty-two cases had minimal ALH (≤3 foci). At follow-up, only 7% had atypical lesions other than ALH, 2 with LCIS and 1 with atypical ductal hyperplasia. Of the cases with >3 foci of ALH, all had atypical follow-up excisions with 9 cases of ALH, 4 cases of LCIS, and 1 of atypical ductal hyperplasia. Of the 12 cases of LCIS with follow-up excision, 3 had infiltrating carcinoma, 2 had ductal carcinoma in situ, and 3 had ALH.

**Conclusions:** The authors conclude that cases of ALH seen on core biopsy need not have follow-up excision if <3 foci of the disease are seen and there are no discordant clinical or radiographic features.

**Reviewer's Comments:** Even cases with more extensive ALH were not associated with anything worse than atypical ductal hyperplasia on follow-up. One does wonder, though, how reproducible the distinction between ALH and LCIS is in all cases. (Reviewer-Edward B. Stelow, MD).

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Keywords: Core Biopsy, Atypical Lobular Hyperplasia, Lobular Carcinoma In Situ

Print Tag: Refer to original journal article
Cellular dyscohesion in melanoma with vertical growth phase is associated with local recurrence and metastatic disease.

**Background:** Malignant melanoma, especially when in vertical growth phase, has a high metastatic potential with high mortality rate. The single most significant histological prognostic factor is the depth of invasion (Breslow thickness), but the American Joint Committee on Cancer TNM classification also accounts for ulceration and level of dermal invasion (Clark level). Many other prognostic features have been described that represent functional characteristics reflecting the complex progression to metastasis, such as ulceration representing the capacity to breach the overlying epidermis. Melanoma cells have been shown to have altered cellular adhesion molecules and disturbed cellular interactions, including loosening of adhesion to neighboring cells, which could have implications for metastatic potential.

**Objective:** To determine whether a cellular dyscohesion score has prognostic value.

**Methods:** All cases of melanoma were reviewed to include only those in vertical growth phase, defined as dermal nests larger than junctional nests or >20 to 25 cells across, usually with mitotic figures present. The Breslow thickness, ulceration, regression, and clinical follow-up were documented. Cohesion was assessed in the invasive component, and gaps between cells that exceeded the diameter of the cell were considered dyscohesive. Gaps less than the diameter of the cells were considered retraction artifact. Dyscohesive cells were also noted to have random arrangements of the cell membranes and cytoplasmic processes. Cohesive cells with retraction artifact were noted to have parallel arrangement of the cell membranes. Singly dispersed cells were considered dyscohesive. Each case was scored for the dyscohesive component: 1 for 0% to 25%; 2 for 25% to 50%; 3 for 50% to 75%; and 4 for 75% to 100%.

**Results:** 48% of the tumors were scored as 1, 16% as 2, 19% as 3, and 17% as 4. Dyscohesion correlated with local recurrence or metastatic disease, and this was especially significant for dyscohesion score 1 versus >2. T1 to T3 staged melanomas with a score of 1 had a significantly higher survival rate. The extent of dyscohesion was independent of Breslow thickness or regression.

**Conclusions:** Dissociation of malignant cells may be a step in tumor progression to metastatic disease. Assessing the percent of malignant melanocytes with cellular dyscohesion may provide prognostic information that appears independent of Breslow thickness.

**Reviewer's Comments:** It is plausible that cells need to first dissociate from each other in order to metastasize from the primary site. (Reviewer-Mary T. Galgano, MD).

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Keywords: Melanoma, Cellular Cohesion

Print Tag: Refer to original journal article
Merkel Cell Carcinoma: Incidence, Mortality, and Risk of Other Cancers.

Kaae J, Hansen AV, et al:

J Natl Cancer Inst 2010; 102 (June 2): 793-801

Merkel cell carcinoma occurs mostly in elderly individuals in sun-exposed skin.

**Background:** Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin. Recently, it was shown to be related to infection with a virus, the Merkel cell polyomavirus (MCV). The tumors occur in sun-exposed individuals and are more likely to occur in individuals who are immunocompromised. It has also been noted that they are more likely to occur in individuals with hematologic malignancies.

**Objective/Design:** This study used a population database to study the incidence, mortality, and risk for other cancers in patients who develop MCC.

**Methods:** Nearly 30 years of results were collected from the Danish Cancer Register, which is believed to capture between 90% and 95% of all incident cancers in Denmark. All MCCs and other skin cancers were identified, and HIV/AIDS status was also gathered. Incidence rates and mortality rates were calculated. Incidence of other cancers was gathered.

**Results:** 185 diagnoses of MCC were made over nearly 30 years. More than 90% of patients were >65 years of age, and almost 60% were at least 75 years old. Nearly 50% of the tumors occurred in the head, and the remaining tumors were relatively evenly distributed on the upper limbs, lower limbs, and trunk. More than half of the patients had localized disease, 20% had metastases, and 25% were not staged. No patients had HIV or AIDS, but the incidence of this disease in Denmark is very low. The incidence rate of MCC was 2.0 and 2.4 per million people-years for men and women, respectively. The increased incidence in women was found to be secondary to longer life spans. Male patients were twice as likely as female patients to die of disease. Matched for age, 33% of patients without MCC were expected to die within 5 years compared to 55% and 84% of patients with localized and nonlocalized MCC, respectively. Patients diagnosed with MCC were more likely to have been diagnosed with squamous cell carcinoma of the skin, basal cell carcinoma, melanoma, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma. Patients with MCC were also more likely to be diagnosed with squamous cell carcinoma and chronic lymphocytic leukemia after their diagnosis than other people of the same age.

**Conclusions:** MCC is a disease of older individuals that occurs mostly in sun-exposed skin, often with other skin cancer. Its relationship to hematologic malignancy is interesting and may be secondary to immunocompromised states.

**Reviewer's Comments:** This paper shows the advantages of a national cancer database for epidemiologic studies. In spite of the association with viral infection, it is interesting to note how related to sun exposure MCC appears to be. (Reviewer-Educator B. Stelow, MD).

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Keywords: Merkel Cell Carcinoma, Incidence, Mortality, Comorbidity

Print Tag: Refer to original journal article
Higher WT 1 Expression Seen in Advanced Stages of Melanoma

WT 1 Expression in Nevi and Melanomas: A Marker of Melanocytic Invasion Into the Dermis.

Garrido-Ruiz MC, Rodriguez-Pinilla SM, et al:

J Cutan Pathol 2010; 37 (May): 542-548

Cytoplasmic expression can be seen in both nevi and melanomas and is associated with advanced stages of melanomas, with decreased overall survival.

**Background:** WT 1, a tumor suppressor gene, is fundamentally involved in a variety of normal tissues and tumors. Many of these tumors are derived from tissues that do not normally express WT 1. Furthermore, no mutations have been found in the WT 1 gene derived from tumors, and in some tumors, higher levels of expression correlate with poorer prognosis. Thus, although a tumor suppressor, WT 1 might be more akin to an oncogene in tumor biology.

**Objective:** To access WT 1 expression and possible clinical significance in benign and malignant melanocytic lesions.

**Methods:** Tissue samples comprised of nevi and primary melanomas were identified retrospectively. Survival analysis was restricted to patients with melanoma only. A tissue microarray was constructed, and cases were stained with WT 1 and positivity set at >10%. Statistical analysis was then performed on IHC and survival data.

**Results:** The cases included 163 primary melanomas and 108 nevi. Half of the melanomas included the superficial spreading type, but all histologic subtypes were well represented. The nevi consisted of compound or intradermal nevi, congenital nevi, Spitz, and atypical nevi. The median follow-up time for the melanoma cases was 120 months. In total, approximately 51% of benign nevi and 40% of melanomas stained (cytoplasmic) with WT 1. Intradermal and Spitz nevi expressed WT 1 in significantly more cases than with congenital and atypical nevi. Regarding melanoma cases, there was significantly more WT 1 expression with melanomas in vertical growth phase, higher Clark levels, and thicker lesions. There was no significant expression difference between cases with ulceration, vascular invasion, primary tumor size, or microscopic "satellites." There was also no significant difference among gender or age range. Follow-up data on 74 patients showed a statistically significant association between shorter overall survival and positive WT 1 expression.

**Conclusions:** WT 1 expression is usually nuclear in tumors such as Wilms's tumor and mesothelioma. The aberrant cytoplasmic localization may indicate an alteration in the properties of the neoplastic cells, suggesting a role in differentiation and dedifferentiation. In this study, cytoplasmic WT 1 expression can be found in both nevi and melanomas, with higher expression in advanced stages of melanoma, with poorer overall survival.

**Reviewer’s Comments:** This paper touches on a very interesting hypothesis in tumor biology; namely, that WT 1 may function as a tumor suppressor in some tissues and an oncogene in others. This explains why there is staining in benign nevi and melanomas and differential staining within these groups. WT 1 could be a potential antigen to be targeted in medical therapy. (Reviewer-William A. Kanner, MD).

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Keywords: WT 1, Nevi, Melanoma, Melanocytic Invasion, Dermis

Print Tag: Refer to original journal article
**Background:** The concept of the tumor microenvironment is a very important topic in dermatopathology, especially concerning malignant melanoma. The concept is that cancer cells may evoke an immune response by both the innate and adaptive immune system and depending on the response, may lead to tumor progression or inhibition.

**Objective:** To highlight evidence of antitumor immune responses in the context of malignant melanoma.

**Results:** **Prognostic Importance of Intratumoral Lymphocytes.** Focusing on melanoma, it has been shown that melanoma can elicit a significant dermal lymphocytic reaction, leading to partial tumor destruction. Clonal T-cell expansions have been documented in primary regressing melanoma, and in many patients, CD4+ and CD8+ cells that react with melanoma cells can be detected in the blood, lymph nodes, and metastases. Of clinical importance is that it has been shown that dense intratumoral (but not peritumoral) T-cell infiltrates have been correlated with prolonged survival and decreased incidence of metastatic disease in patients with vertical growth phase melanoma. In fact, similar correlations have been seen with many other neoplasms. However, disease development is not prevented, and research has focused on regulatory T-cells (Tregs, FoxP3+) suppressing the immune response as well as the PD-1/PD-L1 costimulatory pathway. **Therapy-Induced Antitumor Immune Response.** With this background, clinical trials have already been undertaken. In one Phase I trial, stage IV metastatic melanoma patients were vaccinated with irradiated, autologous melanoma cells engineered to secrete granulocyte–macrophage colony-stimulation factor (GM-CSF). This vaccination elicited an immunologic response that resulted in dense inflammatory infiltrates with significant tumor destruction (at least 80%). While this response was impressive, most immunized patients eventually succumbed to progressive disease. Thus, additional immunologic defects remain, and further research implicates cytotoxic T-lymphocyte associated antigen-4 (CTLA-4). It appears that CTLA-4 is required for Treg function. Thus, the authors of this manuscript administered anti–CTLA-4 mAb to 14 metastatic melanoma patients who had been previously immunized. Again, a significant response was noted, and 10 patients achieved clinically meaningful antitumor effects.

**Conclusions:** Ongoing studies are elucidating the pathways involved in the immune mediated response to tumors.

**Reviewer's Comments:** This is one of a series of articles from this issue of the *Journal of Cutaneous Pathology* highlighting the significant contributions that Dr. Martin Mihm has made in dermatopathology. The tumor microenvironment is really a "hot topic" in research right now and will hopefully yield clinically useful data. (Reviewer-William A. Kanner, MD).

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Keywords: Melanoma, Tumor Microenvironment, Tumor-Infiltrating Lymphocytes

Print Tag: Refer to original journal article
The *Streptococcus pneumoniae* urinary antigen test is approximately 65% sensitive in detecting *S. pneumoniae* bacteremia.

**Background:** *Streptococcus pneumoniae* (SP) is the most common cause of pneumonia, and in nearly one-third of cases, routine diagnostic methods will fail to identify an organism. In 1999, the FDA approved the use of Binax NOW, an immuno-chromatographic urinary antigen test (UAg) to detect all pneumococcal serotypes. It has been advocated as a useful test in evaluating adults with community-acquired pneumonia because of its rapidity, simplicity, and reasonable specificity (80% to 100%) and sensitivity (55% to 92%). However, little information is available regarding the performance of SP UAg testing to detect SP bacteremia.

**Objective:** To evaluate the sensitivity of SP UAg to detect bacteremia and its relationship with renal function and severity of disease.

**Design:** Retrospective study.

**Methods:** Adults with SP bacteremia diagnosed by duplicate sets of blood cultures that also had SP UAg testing performed were included. The SP UAg test was performed according to the manufacturer's directions, using unconcentrated urine. Renal function was calculated using serum creatinine to calculate the glomerular filtration rate (GFR); a GFR ≥60 was considered good renal function, and a GFR <60 was considered impaired renal function. The grade of bacteremia was divided into high grade (≥3 bottles positive for SP) or low grade (<2 bottles positive). The patient's severity of illness was calculated using CURB-65 scores; a score ≤2 indicated a low to intermediate risk of mortality, and a score >2 indicated a high risk of mortality.

**Results:** 65 patients had SP bacteremia and SP UAg testing during the study period. SP UAg testing was positive in 42 patients (65%). Impaired renal function was present at the time of UAg testing in 35 patients; SP UAg was positive in 77% of patients with renal impairment versus 50% of those without renal impairment. High-grade bacteremia was present in 41 patients; SP UAg was positive in 71% of patients with high-grade bacteremia compared to 47% of those with low-grade bacteremia. A high risk of mortality by the CURB-65 score was present in 39 patients; SP UAg was positive in 76% of patients with a high risk of mortality versus 50% of those with a low risk of mortality. On multivariate analysis, only renal impairment was associated with increased detection of SP UAg.

**Conclusions:** The performance of SP UAg testing to detect SP bacteremia is less sensitive than previously published. Interestingly, impaired renal function had a significant impact on test outcome.

**Reviewer's Comments:** The relationship of renal function and test outcome is interesting. Impaired renal function may be a surrogate marker of disease severity. However, most of the patients had reversible impaired renal function, suggesting instead that it is a marker of urine concentration (due to dehydration). The manufacturer has previously demonstrated that serial dilution of urine decreases the test's sensitivity.

(Reviewer-Deborah J. Chute, MD).

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Keywords: *Streptococcus pneumoniae*, Urinary Antigen, Bacteremia, Diagnosis

Print Tag: Refer to original journal article
Ovarian embryonal carcinomas are strongly and diffusely positive for OCT4 and are frequently positive for CD30.

**Background:** Ovarian embryonal carcinoma (EC) is rare and most commonly occurs in the setting of a mixed germ cell tumor. EC can be difficult to identify and has many mimics, including other germ cell tumors and non-germ cell malignancies.

**Objective:** To examine the morphologic and immunohistochemical features of a series of ovarian ECs, along with 4 additional cases that were initially misinterpreted as EC.

**Methods:** 6 cases of ovarian mixed germ cell tumors with an EC component were retrospectively reviewed. An additional 4 cases originally diagnosed as EC, which were reassessed as other germ cell tumor types, were reviewed as mimics of EC. H&E sections from each case were examined, and the tumor growth patterns and any co-existing germ cell components were recorded. Immunohistochemical staining was performed on each case with antibodies against OCT4, CD30, glypican 3, and SOX2. Tumor cells were considered positive when membranous staining was present for CD30 and glypican 3, and if nuclear staining was present for OCT4 and SOX2. Finally, FISH analysis for chromosome 12p abnormalities was performed on each case.

**Results:** Morphologically, EC was characterized by primitive cells with large, pleomorphic, vesicular nuclei that had prominent nucleoli and significant nuclear overlap. These cells formed sheets, pseudo-glandular spaces, and occasionally papillae. EC was most commonly found in association with yolk sac tumor (5 of 6) and dysgerminoma (4 of 6). In all EC cases, the tumor cells showed strong and diffuse OCT4 staining. Variable CD30 staining was present in most cases (5 of 6). Glypican 3 was positive only in areas morphologically consistent with yolk sac tumor. SOX2 staining was present in 3 of 6 ECs. Chromosomal 12p abnormalities were present in 5 of 6 EC cases. The most common mimics of EC were the solid variant of yolk sac tumor (2 cases) and primitive neuroectodermal components of immature teratomas (2 cases). Differentiating solid yolk sac tumor from EC was best determined by the absence of OCT4 and CD30 staining and the presence of glypican3. Immature teratomas were more likely to cause substantial difficulty; the primitive neuroectodermal components were partially positive for OCT4. However, the neuroepithelium was consistently negative for CD30 and also demonstrated glial tissue and neuroepithelial rosettes, and was positive for neural markers such as neurofilament.

**Conclusions:** Ovarian embryonal carcinoma is most commonly confused with the solid variant of yolk sac tumor and primitive neuroepithelial components of immature teratoma. A panel of immunohistochemical stains, including OCT4, CD30, and glypican 3, is useful in confirming the diagnosis.

**Reviewer's Comments:** In the majority of cases, a well-prepared H&E slide is adequate for diagnosing embryonal carcinoma. However, in difficult cases, immunohistochemistry is useful. Pathologists should be aware of the potential mimics of embryonal carcinoma, particularly the solid variant of yolk sac tumor and immature teratoma. (Reviewer-Deborah J. Chute, MD).

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Keywords: Ovary, Germ Cell Tumors, Embryonal Carcinoma, Yolk Sac Tumor, Teratoma, OCT4, FISH

Print Tag: Refer to original journal article
Background: Chemokines act to recruit and direct the migration of leukocytes to areas of injury and to drive the inflammatory process. It is thought that high chemokine levels combined with an inability to resolve inflammation may contribute to tissue pathology in the setting of solid organ transplantation. So-called "decoy" chemokine receptors are similar to usual chemokine receptors in their structure and high-affinity ligand binding, but they lack signalling ability. D6, one such decoy receptor, suppresses inflammation by scavenging various proinflammatory chemokines. While some studies have examined the expression of other decoy receptors in cases of renal allograft rejection, no studies investigating D6 in allograft rejection have been reported.

Objective: (1) To assess the role of D6 in allograft rejection by examining the expression of D6-binding chemokines and D6 protein in cardiac allograft biopsies; (2) to identify possible regulators of D6; and (3) to show how D6 upregulation may modulate inflammation in the setting of rejection.

Methods: Confocal microscopy was used to examine D6 expression in graft-infiltrating leukocytes in 19 cardiac allograft biopsies. In vitro studies were performed to assess cytokine regulation of D6, and a chemokine scavenging assay was performed to show, in part, how D6 modulates inflammation.

Results: D6 was predominantly found associated with graft-infiltrating leukocytes (CD45+/CD68+). A significantly higher level of D6 expression was identified in cardiac allografts showing more severe rejection. In vitro studies showed that transforming growth factor-β (TGF-β) increased D6 expression by monocytes. This increase, in turn, was associated with enhanced chemokine scavenging.

Conclusions: The decoy chemokine receptor D6 can be detected in cardiac allograft tissue. Its expression is altered depending on the severity of rejection, and its expression can be regulated by TGF-β.

Reviewer's Comments: Currently, the assessment of cardiac allograft rejection relies on the histologic examination of endomyocardial biopsy specimens. In recent years, the use of immunofluorescence or immunohistochemistry to detect the expression and distribution of C4d has shown some value in helping distinguish cell-mediated from antibody-mediated rejection mechanisms. Markers such as the D6 decoy chemokine receptor will undoubtedly be used in addition to histologic assessments to better refine the type and nature of rejection in cardiac allografts. (Reviewer-T. David Bourne, MD).

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Primary ovarian malignant melanoma is a very rare tumor that shows a variety of histologic patterns.

**Background:** Primary ovarian malignant melanoma is an extremely rare neoplasm, with only approximately 30 documented cases reported since 1901. The diagnosis is challenging due to the rarity of the tumor and its phenotypic variability.

**Objective:** To report and describe the clinical and morphologic features of primary ovarian malignant melanoma.

**Methods:** 5 cases of reported primary ovarian malignant melanoma were retrieved from the department archives. Study material included cases that had been sent from outside institutions for consultation review. Medical records were reviewed to obtain pertinent clinical and demographic information. Gross findings were obtained from surgical pathology reports. Slides from each case were reviewed, and various histologic features were recorded. Immunohistochemistry (IHC) for S100, HMB-45, and Melan-A were performed in most cases. Electron microscopy (EM) was performed in 2 cases. Features considered suggestive of primary ovarian malignant melanoma included origin within a cystic teratoma, unilaterality, and absence of an extra-ovarian tumor.

**Results:** Patient ages ranged from 41 to 71 years, and ethnicities included Asian, African American, Caucasian, and Hispanic. Four tumors had origin within teratomas, IHC markers were positive in all tested tumors, and premelanosomes were identified in 2 tumors using EM. Architectural patterns included nodular, diffuse, and mixed nodular and diffuse growth. A pseudopapillary pattern associated with necrosis and a pseudoglandular pattern associated with hemorrhage were also observed. Features characteristic of melanoma included spindle cells, epithelioid cells, melanin pigment, prominent nucleoli, and intranuclear pseudoinclusions. Other features included rhabdoid cells, multinucleated giant cells, necrosis, hemorrhage, and inflammatory infiltrates. Sites of metastasis included regional lymph nodes, omentum, peritoneal surfaces, lung, liver, central nervous system, and bone. All patients died of disease within 18 months.

**Conclusions:** Being familiar with the diagnosis of primary ovarian malignant melanoma and its various morphologic and cytologic features will help facilitate the recognition of this rare, aggressive tumor.

**Reviewer's Comments:** As in other sites, the diagnosis of malignant melanoma is not always straightforward. It is not surprising that this article emphasizes the importance of IHC and, to a lesser extent, EM as diagnostic aids. The distinction between primary and secondary ovarian melanoma, despite the features suggested here, will continue to be challenging. (Reviewer-T. David Bourne, MD).

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Keywords: Malignant Melanoma, Ovary

Print Tag: Refer to original journal article
Does JCV Have a Role in Gastric Ca?

The Presence of JC Virus in Gastric Carcinomas Correlates With Patient’s Age, Intestinal Histological Type and Aberrant Methylation of Tumor Suppressor Genes.

Ksiaa F, Ziadi S, et al:

Mod Pathol 2010; 23 (April): 522-530

A subset of gastric carcinomas is associated with the JC virus, which may prove to have a role in the tumorigenesis of intestinal-type gastric carcinomas, especially in older patients.

**Background:** Although mostly known for causing progressive multifocal leukoencephalopathy in AIDS patients, the JC virus (JCV) has recently been implicated in colorectal and gastric cancers. JCV is a polyomavirus, as are the BK virus (BKV) and the Simian Virus 40 (SV40), which are all associated with either diseases of immunosuppression or tumorigenesis.

**Objective:** To determine the prevalence of JCV, BKV, and SV40 in gastric carcinomas.

**Methods:** 61 gastric cancer samples from Tunisia were collected with paired normal tissues. PCR was used to detect polyomavirus DNA, and results were compared to p53 expression and methylation status of 11 tumor-related genes.

**Results:** The T-antigen sequence of the JCV was detected in 26% of the gastric cancers and in 6% of the normal control gastric mucosa. BKV and SV40 were not detected in any case. The tumors positive for JCV were from older patients (age >55 years) and were more likely to be intestinal type than were the negative tumors (reaching statistical significance). The tumors associated with JCV were also more likely to have methylation of P16 and P14, and to have a higher mean methylation index than in the JCV-negative tumors. In a multivariate analysis, only the age of the patient and the methylation index were independent factors of gastric carcinomas associated with the JCV. The Kaplan-Meier survival analysis showed a trend toward better survival in patients whose tumors were positive for JCV, but this did not reach statistical significance.

**Conclusions:** A subset of gastric carcinomas is associated with JCV, which may prove to have a role in the tumorigenesis of intestinal-type gastric carcinomas, especially in older patients.

**Reviewer’s Comments:** The authors speculate that older patients have a diminished immune regulation that allows for the active replication of the JCV, leading to the development of malignancy. Regardless, the association with aberrant methylation of tumor suppressor gene suggests a mechanistic role in tumorigenesis. (Reviewer-Mary T. Galgano, MD).

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Keywords: Gastric Carcinomas, JC Virus, Tumor Suppressor Genes

Print Tag: Refer to original journal article
Carcinomas of the endometrium and ovary with undifferentiated components are in the spectrum of undifferentiated carcinomas and should be recognized for a poor prognosis and higher likelihood of microsatellite instability.

Background: Carcinomas of the endometrium and ovary with undifferentiated foci are uncommon but are easily misclassified based on a lack of specific features, or they may be diagnosed as the more differentiated component, if present ("dedifferentiated carcinomas"); however, the diagnosis may confer prognostic and therapeutic implications.

Objective: To present the clinicopathologic features of a series of endometrial and ovarian carcinomas with undifferentiated components, and to evaluate their expression of mismatch repair (MMR) proteins.

Methods: Archived files were searched for undifferentiated carcinomas and dedifferentiated carcinomas of the endometrium and ovary. Slides were reviewed to exclude poorly differentiated tumors with some indication of a specific line of differentiation.

Results: 26 endometrial and 6 ovarian carcinomas were identified. The mean patient age was 55 years (range, 21 to 76 years), and most patients presented at an advanced stage. Twenty of the carcinomas were pure undifferentiated, while 12 were endometrioid type with undifferentiated components. The undifferentiated tumors generally had sheets of dyscohesive ovoid cells with uniform, large vesicular nuclei. Few tumors had focal nuclear pleomorphism or zones of rhabdoid cells in a myxoid stroma. Most tumors had at least focal strong keratin (particularly CK18) and/or epithelial membrane antigen staining. Muscle markers, neuroendocrine markers, and estrogen receptor/progesterone receptor were generally negative. MMR protein expression was assessed in 17 cases, with 7 having lost the expression of MLH1/PMS2 and 1 having lost MSH6. Of 27 patients with follow-up data (median, 9 months), 41% died of disease in <20 months, 4 are alive with disease, and 12 are alive without evidence of disease.

Conclusions: Endometrial and ovarian carcinomas with undifferentiated components should be recognized in the spectrum of undifferentiated carcinomas. These confer a similar poor prognosis, and many show loss of MMR proteins that could represent a heritable cancer syndrome, such as Lynch syndrome.

Reviewer’s Comments: The authors noted that the loss of MMR proteins was observed in both the undifferentiated and differentiated components (when present). This may represent the characteristic of a tumor with microsatellite instability to have continued DNA damage and tumor progression. (Reviewer-Mary T. Galgano, MD).

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Keywords: Carcinoma, Undifferentiated Components

Print Tag: Refer to original journal article
Human papillomavirus-induced squamous cell carcinoma of the tonsil can be undifferentiated, similar to nasopharyngeal carcinoma.

**Background:** Over the past 20 years, we have come to better understand the role of human papillomavirus (HPV) in the development of head and neck cancer. While the virus can be associated with any squamous cell carcinoma within the upper aerodigestive tract, it is particularly related to oropharyngeal carcinoma. It is now believed that between 40% and 80% of all oropharyngeal carcinomas are caused by the virus. Frequently, these squamous cell carcinomas are nonkeratinizing or basaloid in appearance, sometimes with a more exophytic and papillary growth.

**Objective:** To report on a series of oropharyngeal squamous cell carcinomas that show lymphoepithelioma-like growth.

**Methods:** The surgical pathology files of 2 institutions were reviewed for undifferentiated carcinomas of the oropharynx. Also included were metastatic squamous cell carcinomas with undifferentiated growth for which a primary tumor could not be identified. The tumors were defined as those with large tumor cells, indistinct cell borders, round to oval vesicular nuclei, and large central nucleoli. Tumor cells were organized in small nests or as single cells dispersed in a dense lymphoplasmacytic infiltrate without desmoplasia. In situ hybridization for HPV was performed using DAKO or Ventana probes; p16 immunohistochemistry was also performed.

**Results:** 22 tumors were identified from 16 men and 6 women. The median age was 52 years, and the age range was 37 to 85 years. Thirteen patients had never smoked. Fifteen cases presented with an oropharyngeal primary, and 7 presented with cervical node metastases. Of the 7 cases that presented with cervical node metastases, 4 were found to have an oropharyngeal primary. All tumors were immunoreactive with antibodies to p16, and 19 were positive for HPV by in situ hybridization. All cases were negative for Epstein-Barr virus (EBV) by in situ hybridization. Tumors were invariably stage 3 or 4 at presentation. Of the 21 patients with follow-up information who received combination chemotherapy and radiation therapy, none developed recurrence as of their last follow-up.

**Conclusions:** Oropharyngeal squamous cell carcinomas can have a morphology identical to that seen with EBV-associated squamous cell carcinomas of the nasopharynx. These tumors appear to have a good prognosis, similar to those of other upper aerodigestive tract HPV-associated tumors.

**Reviewer’s Comments:** Pathologists need to be aware that HPV-associated tumors can appear undifferentiated. This is important both as primary oropharyngeal samples are interpreted and as metastatic tumors to head and neck lymph nodes are reviewed. (Reviewer—Edward B. Stelow, MD).

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Keywords: Squamous Cell Carcinoma, HPV, Undifferentiated, Oropharynx

Print Tag: Refer to original journal article
There does not appear to be any association between coffee and soda intake and the risk for colorectal adenocarcinoma.

**Background:** Colorectal adenocarcinoma is the third most common cancer in the world. Because rates vary so greatly from place to place, many speculate that environmental influences, especially diet, play a role in its development. Recently, it has been speculated that the polyphenols present in tea and coffee may protect against the development of colorectal adenocarcinomas. Furthermore, the substances may increase colonic motility, which may further decrease the risk of colorectal adenocarcinoma. Epidemiologic evidence is mixed, however, and some even speculate that these substances may be mutagenic and increase the risk of the development for colorectal adenocarcinoma. Finally, the consumption of sweetened soft drinks has been suggested to be a risk factor for the development of colorectal adenocarcinoma since it is so closely related to obesity and diabetes.

**Objective:** This study represents a pooled analysis of the risks for these drinks in the development of colorectal adenocarcinoma.

**Design:** 13 prospective cohort studies were identified that had >50 incident cases of colorectal adenocarcinoma, a publication on dietary intake and cancer association, and a comprehensive dietary assessment. The quantity of beverage consumption was compared to the risk of development of colorectal adenocarcinoma.

**Results:** Within the 13 studies, there were >5500 incident cases of colorectal adenocarcinoma. Slightly more cases occurred in the proximal colon. At least 70% of participants in each study drank coffee, with significant differences in individual consumption. Coffee drinking was not found to be associated with colorectal cancer risk, and the relative risk was 1.07. There was a 1.28 relative risk for the development of colorectal adenocarcinoma in persons who drank tea. Only one of the studies, however, showed a significant relationship between tea consumption and colorectal adenocarcinoma risk. The consumption of sugar-sweetened carbonated beverages was not associated with a risk of colorectal adenocarcinoma, and the overall relative risk for consumers was found to be 0.94. There was no association with increased consumption of the beverage. Finally, overall caffeine intake was not associated with a risk of colorectal adenocarcinoma.

**Conclusions:** Drinking sugar-sweetened soft drinks and coffee is not associated with a risk of developing colorectal adenocarcinoma. The authors believe the possible association with tea consumption needs to be further investigated.

**Reviewer's Comments:** Pathologists can continue to drink coffee and sugar-sweetened beverages without having to worry about excess risk of developing colon cancer. This is especially good news for those of us who do not typically get enough sleep. (Reviewer-Edward B. Stelow, MD).