Both leukocyte reduced products and cytomegalovirus (CMV)-seronegative products significantly reduce transfusion-transmitted CMV. However, transfusion practices vary widely among blood banks.

**Background:** Cytomegalovirus (CMV) is a common and significant pathogen that can be transmitted via blood transfusion. In the chronic carrier state, latent virus resides in certain peripheral white blood cells. To reduce the risk of transfusion-transmitted CMV (TT-CMV), either (1) blood components must be collected from CMV-seronegative donors, or (2) leukocyte-reduced (LR) blood components must be used. The former is a significant challenge to accomplish due to the high prevalence of CMV in the donor population. The latter practice has been shown to reduce the transmission rate comparable to that of CMV-seronegative units. The American Association of Blood Banks (AABB) published guidelines stating that LR products reduce TT-CMV to a level at least equivalent to that observed with CMV-seronegative components. However, others have challenged this, and as such, there currently is no consensus on the preferred approach to prevent TT-CMV in various patient populations.

**Objective:** To collect information via a survey on the various transfusion medicine practices regarding the prevention of TT-CMV.

**Methods:** In 2007, a survey was sent to AABB physician members at various institutions throughout the United States. The individuals first were asked to categorize their institution (blood center, academic, community, etc). Next, a series of questions were provided pertaining to institutional blood bank practices regarding the issue of TT-CMV. These corresponded to the various clinical scenarios, especially for at-risk patients (pediatric, transplant, hematologic/oncology patient populations).

**Results:** Approximately 65% of respondents indicated that they believed LR and CMV-seronegative donor products were equally effective at reducing TT-CMV, while the remainder (35%) stated that these products were not equally effective. By institution, 71% of academic centers, 66% of community hospitals, 47% of government institutions, and 61% of community blood centers considered both products equally efficacious. Among specific patient populations, fetal and neonatal patients were more likely than other populations to receive CMV-seronegative blood. Regarding hematopoietic stem cell and bone marrow transplant patients, the data were again mixed. In the solid organ transplant patient population, however, two-thirds of respondents considered LR products equivalent to CMV-seronegative products.

**Conclusions/Discussion:** These results highlight that there is no uniform practice for the prevention of TT-CMV, which applies to both specific patient populations and among various institutions. There were reported inconsistencies between institutional philosophies and transfusion practices in some instances. In the specific populations, long-standing transfusion practices and dogma will be difficult to change without compelling data.

**Reviewer’s Comments:** This article addresses a topic that is well-known to the transfusion medicine service, both in the academic and community setting. Furthermore, the authors highlight the variability in transfusion practices “across the board.” Therefore, more compelling data or more specific guidelines are needed to guide transfusion practice to reduce TT-CMV. (Reviewer-William A. Kanner, MD)

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Keywords: Cytomegalovirus, Blood Transfusion, Transmission Risk

Print Tag: Refer to original journal article
Molecular testing of thyroid fine-needle aspiration interpreted as “follicular lesion/atypia of undetermined significance” was highly specific (100%) but only moderately sensitive (63%) in detecting malignancy.

Background: The Bethesda 2007 Thyroid Cytology Classification created a new diagnostic category for thyroid fine-needle aspiration (FNA) diagnosis: “follicular lesion of undetermined significance/atypia of undetermined significance” (FLUS/AUS). The risk of malignancy in this category is estimated to be 5% to 10%, and therefore, a repeat FNA procedure is generally recommended. Recently, molecular testing in thyroid FNA specimens has been proposed as an ancillary test in the triaging of these patients.

Objective: To evaluate the utility of molecular testing to predict malignancy in thyroid FNA specimens with a diagnosis of FLUS/AUS.

Methods: All thyroid FNA specimens were collected prospectively for molecular testing at the University of Pittsburgh. After direct smears were created, residual FNA material was collected directly into nucleic acid preservative solution and was snap frozen for analysis. Thyroid FNA reports were searched for cases with features of FLUS/AUS during a 31-month study interval. Mutational analysis was performed on each specimen for BRAF, NRAS, HRAS, and KRAS abnormalities using real-time PCR, and for RET/PTC1, RET/PTC3 and PAX8/PPARY gene rearrangements using reverse transcriptase PCR. The molecular results were compared with repeat FNA results and thyroid resection specimens.

Results: The diagnosis of FLUS/AUS was made in 20.5% of all thyroid FNAs, of which 11% had inadequate material for molecular testing. Adequate material for molecular testing and follow-up resection specimens was available for 100 patients with 117 samples. The final diagnosis was papillary thyroid carcinoma (PTC) in 19 patients (14 follicular variant, 4 classic, and 1 tall cell variant). A molecular alteration was found in 12 cases, all of which had a diagnosis of PTC. The most common molecular alteration was NRAS mutation (8 cases), with less commonly BRAF mutations (3 cases) and PAX8/PPARY rearrangement (1 case). Of 49 patients who underwent a repeat FNA before surgery, 8 were diagnosed with PTC. The repeat FNA triaged all patients with carcinoma to surgery, of which 3 were negative for molecular alterations. The estimated sensitivity and specificity of repeat FNA to detect malignancy were 100% and 17%, respectively.

Conclusions: Testing for molecular alterations common in thyroid neoplasms was highly specific but only moderately sensitive in detecting malignancy for patients with an FNA result of FLUS/AUS.

Reviewer’s Comments: Although the use of molecular testing in the triage of thyroid FNA specimens is far from the routine practice of cytology, this intriguing study demonstrates its potential. It should be noted that this study only evaluated cases with surgical excision. Therefore, the true sensitivity and specificity are unknown because many patients will not be triaged to surgery if they have negative molecular testing and a benign repeat FNA. (Reviewer-Deborah J. Chute, MD).

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Keywords: Follicular Lesion of Undetermined Significance, Molecular Testing

Print Tag: Refer to original journal article
Subtyping Helps Establish Behavior for Metaplastic Carcinomas

Breast Carcinoma With Chondroid Differentiation: A Clinicopathologic Study of 21 Triple Negative (ER–, PR–, Her2/neu–) Cases.

Gwin K, Wheeler DT, et al:


Metaplastic carcinoma with chondroid differentiation is a rare breast tumor, but it is a carcinoma variant associated with an aggressive clinical course.

**Background:** Metaplastic carcinomas of the breast are rare, and they consist of a heterogeneous group of tumors characterized by a mixture of adenocarcinoma and areas of squamous or mesenchymal differentiation. Most also have a basaloid phenotype. Metaplastic carcinoma with chondroid differentiation, in particular, is defined as an infiltrating ductal adenocarcinoma with areas of chondroid (cartilaginous) differentiation.

**Objectives:** To describe the clinical and pathological features of metaplastic breast carcinomas with chondroid differentiation.

**Methods:** 21 cases of metaplastic breast carcinoma with chondroid differentiation (World Health Organization 2003 system) were retrieved. Each case was submitted for H&E slide review, tumor grading (Nottingham), and documentation of the presence or absence of ductal carcinoma in situ (DCIS), squamous differentiation, and necrosis. Immunohistochemical (IHC) staining was performed on selected cases using antibodies against ER, PR, HER2/neu, AR, EGFR, S100, calponin, AE1/AE3, and p63. Demographic information, tumor size, lymph node status, pTNM at initial diagnosis, and follow-up and outcome data (when available) were collected.

**Results:** The mean patient age was 49.7 years. Ten patients had a palpable mass, and 1 patient had an enlarged axillary lymph node at presentation. No evidence of distant metastasis was identified in any case. Two patients were BRCA1 mutation carriers. Tumors had a mean size of 2.4 cm, and most were solid and well-circumscribed with central areas of softening. Microscopically, 2 morphologic tumor types were observed. The more common type consisted of a well-defined myxochondroid mass with more cellular peripheral areas containing the infiltrating carcinoma. Central infarction and necrosis were usually prominent. The less common variant showed conventional infiltrating carcinoma with patchy areas of chondroid differentiation. About 43% of all tumors contained intermediate to high-grade DCIS, 38% showed focal squamous differentiation, and no cases showed microcalcifications. IHC analysis showed that, with 1 exception, all cases exhibited a triple-negative profile (ER–, PR–, and HER2/neu–) and AR negativity. Positive lymph nodes were present in 45.5% of the 11 cases available for review. Of these, 60% showed chondroid differentiation. Among the 10 cases with follow-up information, 5 developed distant metastases, 1 had local recurrence, and 4 were alive without evidence of recurrent or metastatic disease.

**Conclusions:** Metaplastic carcinoma with chondroid differentiation represents a distinct subtype of mammary carcinoma. This subtype is associated with aggressive clinical behavior, including frequent metastasis and local recurrence, despite chemoradiation therapy.

**Reviewer's Comments:** As stated by the authors, previous reports have used the term “matrix producing carcinoma” to designate the above cases as well as those showing osseous differentiation. Although the practice of separating tumors based on the presence of cartilaginous versus osseous elements seems justified, the practical utility of further subtyping the tumors with chondroid differentiation is less clear. (Reviewer-T. David Bourne, MD).

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Keywords: Breast Metaplastic Carcinomas, Chondroid Differentiation, Triple-Negative Breast Cancer

Print Tag: Refer to original journal article
Many triple-negative breast cancers are basal-like, and immunohistochemical stains can be used to define this subset.

**Background:** Triple-negative (TN) breast cancers are defined by tumors negative for expression of estrogen and progesterone receptors and HER2-negative. They generally present with adverse clinicopathologic features and confer an aggressive clinical course, due in part to lack of treatment options. They have considerable overlap with basal-like breast carcinomas, which tend to be TN, but were subtyped via grouping of distinct molecular profiles. The basal-like carcinomas express basal keratins, which may allow immunohistochemical (IHC) identification from non-basal-like carcinomas that are TN.

**Objective:** To identify TN breast carcinomas in a large population and to evaluate them for expression of basal keratins with comparison to molecular classification of basal-like carcinomas.

**Methods:** 7048 breast carcinomas were reviewed for documented ER, PR, and HER2 status. Of these, 767 were TN (11%) and were reviewed for clinicopathologic features. Among these TN lesions, 653 had tissue available for IHC and remained TN after repeat testing. Sixty-one tumors previously classified by molecular profiles as basaloid (n=28), cerbB2 (n=13), and luminal (n=20) were similarly subjected to IHC to define the test characteristics of the selected antibodies, which included basal keratins and other markers noted to be relevant in distinguishing phenotypes.

**Results:** The TN breast carcinomas were found mostly in postmenopausal women with high-grade ductal T2 tumors. In the group of 61 carcinomas categorized by molecular profiling, 34βE12 had a high sensitivity (70%) but low specificity (55%) for the basal phenotype. Other single markers had high specificity but lower sensitivity. Thus, a combination of markers was evaluated by ROC curves to best identify the basal phenotype. The triple panel of CK14, EGFR, and 34βE12 provided 100% specificity and 78% sensitivity. When this panel was applied to the entire TN cohort, 84% (n=549) expressed the established basal phenotype.

**Conclusions:** From a Singapore hospital, 11% of breast carcinomas had a TN profile, which was associated with aggressive clinicopathologic features. Of the TN tumors, 84% had a basal phenotype as determined by a panel of antibodies, including CK14, EGFR, and 34βE12.

**Reviewer’s Comments:** TN breast carcinomas are aggressive tumors, but the basal phenotype is a distinct molecular entity within this category. Using the proposed panel, we can more easily separate and study this particular group. (Reviewer-Mary T. Galgano, MD).
Patients who have undergone colonoscopy within the past 10 years are less likely to have advanced neoplasia at the time of their second colonoscopy.

**Background:** Colon cancer is the fourth most common cause of cancer death in the world. Colonoscopy allows for the detection and removal of preinvasive lesions and prevents colorectal cancer. In the National Polyp Study, colonoscopy was associated with a 76% to 90% reduction in the number of colorectal cancers that developed in patients with polyps. However, the benefits of colonoscopy in community practice are less clear.

**Objectives:** To determine the prevalence of colon cancer and advanced adenomas in patients who had and had not undergone colonoscopy within 10 years prior to the study.

**Methods:** Patients with a history of colorectal cancer, inflammatory bowel disease, or colectomy were not eligible. Patients who had undergone colonoscopy >10 years before this study were also excluded. During a study interval of approximately 2.5 years, >5000 patients received colonoscopy within the study area. At colonoscopy, patients were asked if they had undergone a previous colonoscopy. Patients were then classified by the most advanced disease present at the time of their colonoscopies. Patients who had undergone colonoscopy within the previous 10 years were compared to patients who had not undergone colonoscopy.

**Results:** After exclusions, approximately 3300 patients were eligible for the study. Of these, about 600 had undergone colonoscopy within the previous 10 years. Patients who had undergone prior colonoscopy were slightly older and were more likely to have first-degree relatives with colon cancer. Advanced adenomas or cancer were found in 6.1% of those having undergone previous colonoscopy and in 11.4% of those who had not undergone previous colonoscopy. Only 1 of the nearly 600 patients who had undergone colonoscopy was found to have cancer compared to 40 of the 2700 patients who had not previously undergone colonoscopy. Results were more dramatic for neoplasia of the left colon and rectum.

**Conclusions:** Advanced colorectal neoplasms are less common in the left colon and rectum in patients who have undergone previous colonoscopy in the community setting.

**Reviewer’s Comments:** It is interesting that the authors focus predominately on “advanced” lesions rather than on the truly remarkable difference in the number of colon cancers between the 2 groups in their study. This study nicely confirms the benefits of colonoscopy demonstrated in clinical trials. (Reviewer-Edward B. Stelow, MD).

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Keywords: Colonoscopy, Carcinoma, Adenoma, Incidence

Print Tag: Refer to original journal article
**Long-Term Prognosis Favorable for NLPHL**

*Nodular, Lymphocyte-Predominant Hodgkin Lymphoma: A Long-Term Study and Analysis of Transformation to Diffuse Large B-Cell Lymphoma in a Cohort of 164 Patients From the Adult Lymphoma Study Group.*

Biasoli I, Stamatoullas A, et al:

Cancer 2010; 116 (February 1): 631-639

Nodular lymphocyte-predominant Hodgkin lymphoma has a very favorable prognosis, even when treated with watchful waiting after surgery.

**Background:** Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare B-cell lymphoma that was only recognized as a distinct clinicopathologic entity from classical Hodgkin lymphoma (cHL) in the last 20 years. Clinically, NLPHL more frequently affects men, is localized at presentation, and has a very favorable prognosis. NLPHL can undergo histologic transformation to diffuse large B-cell lymphoma (DLBCL), but the rate of transformation is not well established.

**Objective:** To evaluate the long-term outcomes of patients with NLPHL and their rate of transformation to DLBCL.

**Methods:** Patients with NLPHL were identified from a national registry from 1973 to 2003 (cases before 1993 were retrospectively classified and entered into the registry). The diagnostic slides in each case were histologically reviewed by a panel of 10 expert hematopathologists, confirming the diagnosis of NLPHL according to the World Health Organization criteria. Subsequent biopsies were similarly reviewed, and a histologic transformation to DLBCL was confirmed if present. Clinical characteristics, including gender, age, stage, ESR, and number of involved lymph node sites were included. First-line therapies included radiotherapy, chemotherapy, or watch-and-wait after surgical resection. The progression-free survival (PFS) and overall survival (OS) rates were calculated, as was the time to histologic transformation.

**Results:** 164 patients diagnosed with NLPHL were included, with a median follow-up of 9.5 years. Disease recurrence developed in 66 patients (40%), of which 13 had progression to DLBCL (12% transformation rate at 10 years). When stratified by therapy, the 10-year PFS and OS rates for patients treated with chemotherapy and/or radiotherapy was 66% and 93%, respectively, compared to 41% and 91%, respectively, for patients treated with watch-and-wait after surgery. On multivariate analysis, histologic transformation to DLBCL was the strongest predictor of poor outcome, with a 10-year OS rate of 76%, regardless of therapy. No clinical or histologic characteristics were predictive of transformation to DLBCL.

**Conclusions:** NLPHL has a very favorable prognosis: even without chemotherapy or radiotherapy, the overall survival at 10 years is >90%. Histologic transformation to DLBCL occurs at a rate of 12% at 10 years, regardless of therapy, and it is a significant predictor of decreased survival.

**Reviewer’s Comments:** It is important to differentiate NLPHL from cHL because the prognosis and therapy are vastly different. This is one of the first studies to evaluate the long-term prognosis of patients with NLPHL who were not given standard cHL therapy. More than 50% of patients who did not receive chemotherapy or radiotherapy achieved long-term complete remission, and those that recurred had an overall survival rate that was similar to those who were initially treated with specific therapy. (Reviewer-Stacey E. Mills, MD).

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Keywords: Lymphocyte-Predominant Hodgkin Lymphoma, Long-Term Results

Print Tag: Refer to original journal article
Disease Stage Best Predictor of Survival in MCC

Merkel Cell Carcinoma Demographics, Morphology, and Survival Based on 3870 Cases: A Population Based Study.
Albores Saavedra J, Batich K, et al:
J Cutan Pathol 2010; 37 (January): 20-27

Gender, site, tumor size, and stage are important predictors of survival in Merkel cell carcinoma.

**Background:** Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma, usually associated with older, usually immunocompromised individuals. Recent studies have identified Merkel cell polyoma virus in most MCCs tested. Although predominantly cutaneous in origin, MCC has been described in many extracutaneous sites. MCC is considered to be an aggressive neoplasm, but there have not been much data in the literature regarding population-based studies of MCC with a large series of patients.

**Objective:** To analyze demographics, morphology, and survival data from a population-based study of patients with MCC.

**Methods:** Data were collected from 1973 to 2006 using the National Cancer Institute’s SEER Program (Surveillance, Epidemiology, and End Results) and analyzed. A pathologic review of cases was not possible, however, the large number of cases was assumed to provide statistical validity. SEER staging has remained constant over time.

**Results:** The results confirm that this is an uncommon neoplasm, with only 3870 cases reported during the study interval. MCC was significantly more common in men (approximately 60% of cases), and almost 95% of cases occurred in Caucasians. In this study, only 1.0% of the MCC were in African-Americans. The incidence of MCC started to increase in 1986, and the further increase in incidence during the last 2 decades is likely due to improved diagnostic techniques. MCC was predominantly found in older individuals (age >70 years). No pediatric cases were identified in this study. The most common sites of involvement, in descending order, included the skin of the head and neck, the upper extremities, lower extremities, and trunk. Of the extracutaneous sites, the salivary glands were the most common sites, followed by the nasal cavity, lip, lymph nodes, vulva, vagina, and esophagus. The 10-year relative survival rates for patients with localized, regional, and distant stages were approximately 71%, 48%, and 20%, respectively. Correlating the survival by age found that patients aged >70 years had the poorest survival rates (approximately 50%). Women were noted to have better 10-year survival rates compared to men (approximately 65% versus 51%). Regarding tumor size, those tumors <2 cm were associated with 10-year survival rates of 61%, while tumors >2 cm had survival rates of 40%.

**Conclusions:** MCC is a rare neoplasm, most commonly found in the skin of the head and neck region in elderly Caucasian individuals. Factors associated with increased survival include female gender, tumor size <2 cm, location in the upper extremities, and most importantly, low-stage disease.

**Reviewer’s Comments:** MCC has been the subject of many recent publications focusing on Merkel cell polyoma virus. However, very little is known about the basic demographics and long-term follow-up data on such patients. These authors analyzed data spanning >30 years! (Reviewer-William A. Kanner, MD).

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Keywords: Merkel Cell Carcinoma, Demographics, Outcomes

Print Tag: Refer to original journal article
Noninvasive encapsulated follicular thyroid tumors have a good prognosis, despite the presence of necrosis or high mitotic activity.

**Background:** Thyroid neoplasms are primarily classified according to nuclear features (papillary or follicular) and the presence of invasion (capsular or vascular). A small subset of thyroid carcinomas demonstrates an insular growth pattern, high mitotic activity, and/or tumor necrosis, and these are designated “poorly differentiated thyroid carcinomas.” The difficulty arises when fully encapsulated thyroid tumors with no evidence of invasion show these same poorly differentiated features. In the absence of invasion, they would traditionally be called “follicular adenomas.”

**Objective:** To determine the impact of high mitotic activity and/or tumor necrosis on the long-term outcome of patients with encapsulated thyroid tumors of follicular cell origin with high-grade features (EFHG).

**Methods:** 25 cases of encapsulated thyroid tumors with adequate histologic sectioning (at least 1 section per cm) were included. Classical papillary thyroid carcinomas were excluded. Each case was evaluated for high mitotic activity (≥5 mitotic figures in 10 high power fields), tumor necrosis (excluding FNA-induced reaction), and the numbers of foci of capsular and vascular invasion. Vascular invasion was considered extensive if ≥4 foci were identified. The patients’ medical records were reviewed for treatment and clinical follow-up data.

**Results:** All 25 cases had either a high mitotic rate (64%) or spontaneous tumor necrosis (56%). Using current classification schemes, 13 cases met criteria for poorly differentiated thyroid carcinoma, 1 case met criteria for follicular carcinoma, 5 cases met criteria for follicular adenoma, and 6 cases met criteria for follicular variant of papillary thyroid carcinoma. Eight cases were completely noninvasive, of which 3 showed necrosis and 6 had a high mitotic rate. The average length of follow-up was 9 years. None of the noninvasive tumors recurred. The extent of angio-invasion was predictive of recurrence, as 33% of patients with extensive vascular invasion relapsed, while none of the patients with focal vascular invasion recurred.

**Conclusions:** Noninvasive EFHGs have an excellent prognosis, even in the presence of tumor necrosis. Complete encapsulation and extent of angio-invasion appear to be key factors in predicting the outcome of thyroid tumors. The authors advocate interpreting noninvasive encapsulated thyroid lesions with tumor necrosis as “follicular carcinomas,” with a note regarding the limited experience but probable indolent behavior. In cases without necrosis but with a high mitotic index, they advocate interpreting these lesions as “follicular adenomas.”

**Reviewer’s Comments:** EFHGs are extremely rare. The first step after recognizing high-grade features in a thyroid lesion should be to submit the entire nodule and thoroughly evaluate the lesion for capsular and vascular invasion. Most tumors will have invasion upon extensive review. (Reviewer—Deborah J. Chute, MD).

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Keywords: Encapsulated Thyroid Tumors, High Mitotic Activity, Tumor Necrosis, Outcomes

Print Tag: Refer to original journal article
In memory clinic practice, amyloid-β(1-42) and Tau are useful cerebrospinal fluid biomarkers to distinguish probable Alzheimer disease patients from control patients.

**Background:** While definitive confirmation of a clinical diagnosis of Alzheimer disease (AD) currently requires neuroanatomic examination of the brain at autopsy, a diagnosis of “probable” AD may be rendered with 80% to 90% accuracy by applying criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). The full clinical workup includes medical history, physical and neurological examinations, screening laboratory tests, psychometric evaluation, electroencephalography (EEG), and brain MRI or CT. Various CSF biomarkers to enhance diagnostic accuracy have been proposed. These include amyloid-β(1-42) (Aβ42) to reflect the principle constituent of the mature neuritic plaque, and hyperphosphorylated tau (pTau) to reflect one of the main components of the neurofibrillary tangle.

**Objectives:** To establish the sensitivity and specificity of assays for Aβ42, total Tau, and pTau in the cerebrospinal fluid (CSF) to distinguish patients with probable AD from patients with subjective memory complaints (SMC) in the setting of a memory clinic.

**Participants:** 379 patients seen during a 6-year study interval at a large AD referral center.

**Methods:** All patients underwent clinical workups according to NINCDS-ADRDA criteria. Based on consensus agreement of a multidisciplinary panel, 131 subjects were classified as having SMC, while 248 were classified as having probable AD. CSF was collected by lumbar puncture and processed per protocol within 2 hours. A small sample was submitted for routine CSF analysis, including total cell count, RBC count, and total protein. Sandwich ELISA tests were then used to measure Aβ42, Tau, and pTau on the remaining CSF. Laboratory surplus CSF specimens were pooled and used as controls.

**Results:** Cutoff CSF values for each of the markers to achieve 85% sensitivity were 550 ng/L for Aβ42, 375 ng/L for Tau, and 52 ng/L for pTau. The corresponding specificity values were 83%, 78%, and 68%, respectively. When combined, the impact of all 3 biomarkers to diagnose probable AD showed a sensitivity of 93.5% and a specificity of 82.7%. Multivariate linear regression analysis showed that pTau conferred no additional value apart from Aβ42 and Tau in discriminating probable AD patients from control patients. Finally, a diurnal variation in levels of Aβ42 was observed in nondemented control subjects.

**Conclusions:** Aβ42 and Tau are useful CSF biomarkers to distinguish probable AD patients from control patients in memory clinic practice. The observed diurnal variation in Aβ42 levels necessitates uniform collection times when establishing institution-specific reference ranges or diagnostic protocols.

**Reviewer's Comments:** Biomarker analysis for AD will likely be requested from clinical labs in the near future. It is interesting that hyperphosphorylated tau (pTau) did not emerge as an independent marker of probable AD in this study. (Reviewer-T. David Bourne, MD).

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Keywords: Alzheimer Disease, Diagnosis, CSF Biomarkers

Print Tag: Refer to original journal article
**Chronic Sclerosing Sialadenitis Is IgG4-Related Disease**

*Chronic Sclerosing Sialadenitis (Küttner Tumor) Is an IgG4-Associated Disease.*

Geyer JT, Ferry JA, et al:


Chronic sclerosing sialadenitis appears to be within the spectrum of IgG4-related diseases.

**Background:** Chronic sclerosing sialadenitis is uncommon. It typically involves the submandibular gland and presents as a mass, also known as a Küttner tumor. It presents in middle-aged to elderly patients and is slightly more common in men. Histologically, it is characterized by sclerosis with marked lymphoplasmacytic inflammation. While there is acinar atrophy, the salivary gland retains its lobular architecture. Obliterative phlebitis is often seen, while lymphoepithelial lesions are not seen. Recently, patients with IgG4-related sclerosing diseases have been described. These lesions have been especially well-described in the pancreas, and authors have noted that the disease is sometimes associated with salivary gland pathology.

**Objective:** To review the clinicopathologic features of a cohort of cases of chronic sclerosing sialadenitis.

**Methods:** A single institution’s pathology database was searched for all cases of chronic sclerosing sialadenitis seen during a 17-year study interval. Control cases of chronic sialadenitis, not otherwise specified, Sjögren syndrome, and lymphoepithelial sialadenitis were also identified. Clinical and follow-up data were retrieved. All histology was reviewed. A tissue microarray was constructed. Immunohistochemistry (IHC) was performed with antibodies to IgG4, IgG, CD20, CD3, Bcl-2, bcl-6, and κ and λ light chains. Elastin staining was performed with some cases.

**Results:** Of the 13 patients identified with chronic sialadenitis, 7 were women. The mean patient age was 61 years. All patients presented with neck masses. Twelve cases involved the submandibular gland, and 3 were bilateral. No patients had sialolithiasis. One patient had generalized sclerosing lesions (including within the pancreas), 1 had a pseudotumor of the lacrimal gland, and 1 had adenopathy. Eight of 13 cases had well-defined and circumscribed lesions of the salivary gland, while the other 5 cases had diffuse glandular involvement. Histology was consistent. Large lymphoid follicles were seen with expanded germinal centers and sheets of plasma cells. Phlebitis was seen in 9 cases. Rare lymphoepithelial lesions were seen in 2 cases. Other chronic sialadenitis cases tended to have less inflammation and some had calculi. No phlebitis was seen with those cases. Plasma cells were uncommon in classic cases of lymphoepithelial sialadenitis. Increased numbers of IgG4-positive plasma cells were seen with all cases of chronic sclerosing sialadenitis, with IgG4 to IgG ratios averaging 0.86. Other cases of chronic sialadenitis had many fewer IgG4-positive plasma cells. No abnormalities were seen with other IHC markers.

**Conclusions:** Chronic sclerosing sialadenitis has increased numbers of IgG4-positive plasma cells and is within the family of IgG4-sclerosing diseases. Sjögren disease is not related to IgG4 disease.

**Reviewer’s Comments:** Recognition of IgG4-related disease within the salivary glands can lead to proper management of patients with steroids. IHC can be used to help distinguish these lesions from other salivary gland inflammatory conditions. (Reviewer-Edward B. Stelow, MD).

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Keywords: Küttner Tumor, IgG4-Related Disease, Immunohistochemistry

Print Tag: Refer to original journal article
Trastuzumab May Not Fight HER2-Positive Endometrial Cancer

Phase II Trial of Trastuzumab in Women With Advanced or Recurrent, HER2-Positive Endometrial Carcinoma: A Gynecologic Oncology Group Study.

Fleming GF, Sill MW, et al:

Gynecol Oncol 2010; 116 (January): 15-20

While almost 12% of endometrial cancers, particularly high-grade subtypes, are HER2-positive, single-agent trastuzumab therapy did not improve survival in this study of women with advanced or recurrent disease.

**Background:** The combination therapy of conventional chemotherapy plus trastuzumab has proven effective in HER2-positive breast cancer, whether detected by protein expression or gene amplification. Gastric cancers have been shown to have HER2-positive rates similar to breast cancer, and randomized trials have demonstrated a survival benefit with the combination therapy of trastuzumab plus conventional chemotherapy. Case reports have presented anecdotal evidence of HER2-positive endometrial cancers responding to trastuzumab, but large-scale or randomized studies have not been performed.

**Objective:** To evaluate the use of single-agent trastuzumab therapy in women with advanced or recurrent endometrial cancer.

**Methods:** Women with stage III or IV or recurrent endometrial carcinoma with measurable disease were eligible for enrollment. HER2 positivity was defined first by 2+ or 3+ overexpression by immunohistochemistry (IHC) or amplification by FISH (Period A), then later amended to require amplification by FISH (Period B). All tumors were reviewed by a centralized Gynecologic Oncology Group Pathology Committee.

**Results:** Of 286 tumors screened for HER2 amplification, 33 were positive (11.5% overall). By tumor subtype, 3 of 8 clear cell carcinomas (38%), 7 of 25 were serous carcinomas (28%), and only 2 of 29 endometrioid carcinomas (7%) were positive. The HER2-positive results of IHC correlated with the results of FISH. Twenty-three women from Period A and 18 from Period B were enrolled and treated with a median of 2 cycles of therapy. No evidence of tumor response was noted in any patient. Three patients had adverse events that were possibly related to therapy: 1 died of myocardial infarction, 1 died with cardiac arrest, and 1 suffered from presumed pulmonary fibrosis. The trial was closed early due to poor enrollment.

**Conclusions:** HER2-positive endometrial carcinomas are more likely to be of clear cell or serous subtypes. Women with advanced or recurrent HER2-positive endometrial carcinomas do not benefit from single-agent trastuzumab therapy.

**Reviewer’s Comments:** Randomized trials of conventional chemotherapy with and without trastuzumab in women with HER2-positive endometrial carcinomas should also be performed because this is how a significant survival benefit was detected in HER2-positive gastric carcinoma therapy. (Reviewer-Mary T. Galgano, MD).

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Keywords: HER2-Positive Endometrial Carcinoma, Trastuzumab

Print Tag: Refer to original journal article
Calcifying fibrous tumors of the stomach appear to be reactive lesions and probably are not related to other soft tissue tumors.

**Background:** Calcifying fibrous tumor is a rare tumor that most often occurs in the abdominal cavity and soft tissue. The tumors are composed of heavily hyalinized fibrous tissue with interspersed bland fibroblastic spindled cells, scattered psammomatous and/or dystrophic calcifications, and a mononuclear inflammatory infiltrate. The etiology of these tumors is unknown, and some have speculated that they arise from inflammatory myofibroblastic tumors, whereas others have speculated that they are reactive lesions.

**Objectives:** To describe the clinicopathologic features of a small series of these lesions localized to the stomach and to review the literature.

**Methods:** The surgical pathology files of a single institution and consultant pathologist were reviewed for all cases of calcifying fibrous tumors. Clinical information was retrieved. All histologic material was reviewed, and immunohistochemistry was performed with antibodies to SMA, desmin, S100, CD117, PDGFRA, ALK1, CD34, and IgG4. KIT and PDGFRA mutation analysis was performed.

**Results:** This study identified 7 cases from 4 men and 3 women. The mean patient age was 53 years. Tumors ranged from 1 to 3 cm in size. Six of the tumors involved the gastric body. Tumors were almost always found incidentally and were almost always centered in the muscularis propria. The tumors were uniformly hypocellular and had lymphoplasmacytic inflammations with occasional lymphoid aggregates. Psammomatous and dystrophic calcifications were typically seen, akin to previous reports. Many of the histologic features were present focally within surrounding tissues. No areas better classified as other soft tissue tumors, such as gastrointestinal stromal tumors or inflammatory myofibroblastic tumors, were present. Tumors were non-reactive with antibodies to SMA, desmin, S100, CD117, PDGFRA, and ALK1. CD34 immunoreactivity was focal and seen in 2 cases. Occasional IgG4-positive plasma cells were seen in most cases. No KIT or PDGFRA mutations were identified in the cases tested. No tumors recurred.

**Conclusions:** The authors speculate that gastric calcifying fibrous tumors are likely reactive lesions and not related to other soft tissue tumors.

**Reviewer’s Comments:** Calcifying fibrous tumors remain somewhat of a mystery. It will be interesting to see whether tumors classified under this rubric represent a number of different entities. It certainly seems that conservative management is best for these lesions. (Reviewer-E dward B. Stelow, MD).

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Keywords: Calcifying Fibrous Tumor, Clinicopathologic Features

Print Tag: Refer to original journal article
Diagnosis of mycosis fungoides is difficult, especially in early-stage disease.

**Background:** Mycosis fungoides (MF), the most common primary cutaneous lymphoma, is a diagnostic challenge. The differential diagnosis is broad, and even with good clinical information and ancillary studies, diagnosis sometimes requires multiple biopsies after prolonged clinical evaluation. Ancillary studies include evaluation of the CD4/CD8 ratio, loss of T-cell antigens, and T-cell gene rearrangement assays.

**Objective:** To evaluate different algorithmic approaches to diagnosing MF.

**Methods:** 78 cases with the final diagnosis based on clinicopathologic correlation and follow-up were evaluated in a blinded fashion using 3 different scoring algorithms. The first was an MF panel by which 4 pathologists reviewed the H&E slides (2 µm thick) and scored them (0 - not MF; 1 - suspicious; 2 - consistent with; 3 - diagnostic). An averaged score of ≥2 was considered diagnostic. The second algorithm was that proposed by Guitart, in which a single pathologist evaluates major histopathologic criteria (infiltrate density, epidermotropism, and lymphocyte atypia) with a score of 0 to 3 (0 – none; 3 - extensive). Additional histopathologic features merit 1 point. A total score of 0 to 2 represents dermatitis or other, 2 to 3 represents atypical lymphocytic infiltrate, 5 to 6 suggests MF, and ≥7 is MF. Finally, the authors evaluated a limited International Society for Cutaneous Lymphoma (ISCL) algorithm. This included scoring for histology, immunohistochemistry, and clonality studies. Clinical scores were not included in this study since this information is not always provided. In early MF cases, sensitivities and specificities were then calculated and the ROC was generated to evaluate the Guitart and ISCL algorithms.

**Results:** 38 cases were diagnosed as MF, 7 cases as parapsoriasis, and the remaining 33 cases had other diagnoses. Clinical follow-up averaged 22 months. Overall, the Guitart algorithm correlated favorably with the MF panel approach. Examining the ROC for accuracy (area under the curve) among the Guitart and ISCL algorithms demonstrated no statistically significant differences.

**Conclusions:** The authors note that there is a lack of clear superiority among the different algorithms and that, especially with early MF, judicious use of ancillary techniques should accompany the H&E examination.

**Reviewer’s Comments:** This article addresses many important aspects of MF. Firstly, the diagnosis has a large differential and often requires long clinical surveillance with many biopsies. Second, there are different algorithms currently in use to evaluate for MF. At the University of Virginia, we use Guitart scores with ancillary studies when appropriate. Finally, the reader should note that MF treatment is stage-based, and early-stage disease is often associated with a good prognosis. (Reviewer-William A. Kanner, MD).

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Keywords: Cutaneous Lymphoma, Mycosis Fungoides, Diagnosis

Print Tag: Refer to original journal article
There is considerable overlap between primary and lymphoma-associated follicular mucinosis, but there are features that are useful in the evaluation of these patients.

**Background:** Follicular mucinosis (FM) represents follicular degeneration with mucin in the hair outer root sheath and sebaceous glands, with an associated mixed inflammatory infiltrate demonstrating folliculotropism. Primary follicular mucinosis (PFM) is a benign idiopathic type presenting in children and young adults and is clinically a spontaneous remitting process. The second and more common form, lymphoma-associated follicular mucinosis (LAFM), occurs in older patients and is associated with mycosis fungoides (MF) or Sézary syndrome (SS).

**Objective:** To study the histochemical properties and type of mucin accumulating in FM and to address criteria to differentiate PFM from LAFM.

**Methods:** 31 cases of histologically diagnosed FM were retrieved. After reviewing the clinical data, the patients were subdivided into 2 groups. Group 1 (PFM) represented patients with no evidence of MF or SS at presentation and did not develop a cutaneous T-cell lymphoma (CTCL). Group 2 patients (LAFM) had evidence of MF or other lymphoproliferative disorder at diagnosis or developed CTCL during the follow-up. All cases were stained with H&E and special stains. Immunohistochemistry (IHC) and T-cell receptor β-chain and γ-chain gene rearrangement analyses were performed when possible.

**Results:** There were 21 patients with PFM and 10 with LAFM. Nine of the 10 LAFM cases were diagnosed with MF. The mean patient age was 39 years for PFM and 54 years for LAFM. The type of mucin in FM was acid (dermal) mucin without evidence of epithelial (neutral) mucin (staining with colloidal iron and Alcian blue and no staining with PAS). The type of mucin was no different between PFM and LAFM. Solitary lesions of the head and neck region were more common in the PFM group. Histopathologically, the lymphocytic infiltrate was more atypical in the LAFM group, with more pronounced nuclear features, increased density, and associated folliculotropism. The deposition of mucin in cystic spaces within hair follicles was more common in PFM. IHC also demonstrated a more prominent CD4:CD8 ratio in the LAFM group. Monoclonal gene rearrangements were also more often associated with LAFM patients. While there were patients in the PFM group with clonal rearrangements, both in this study (n=1) and in another study (n=7), all patients showed no progression to CTCL.

**Conclusions:** There is no single feature to reliably distinguish between PFM and LAFM. However, certain features are useful in evaluating these patients.

**Reviewer’s Comments:** The question is whether PFM and LAFM represent 2 distinct entities or a spectrum of presentations with PFM corresponding to early and localized MF with a good prognosis. This study further evaluates this question, and the reader will note that there are overlapping, yet helpful features in both types of FM. (Reviewer-William A. Kanner, MD).

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Keywords: Follicular Mucinosis, Subtypes, Clinicopathologic Features

Print Tag: Refer to original journal article
The commonly used toxin A/B immunoassay for *Clostridium difficile* infection has a sensitivity of 68% in detecting infection.

**Background:** *Clostridium difficile* colitis is a disease mediated by 2 exotoxins (toxin A and toxin B), which are encoded by the *tcdA* and *tcdB* genes. Because *C difficile* remains a significant cause of hospital-acquired diarrhea, accurate and rapid testing is required for infection control. Most laboratories use an immunoassay that detects preformed toxin A or toxin B because direct culture and cytotoxic assays are labor-intensive and slow. However, recent papers have suggested that the Premier™ *C difficile* Toxin A/B Assay (PTAB) is less sensitive and specific than previously thought. Instead, a 2-step algorithm incorporating an immunoassay to detect the *C difficile* common antigen GDH, with either cytotoxin or polymerase chain reaction (PCR) testing as confirmatory methods, has been suggested.

**Objective:** To evaluate the performance of the PTAB immunoassay compared to a GDH antigen immunoassay for the detection of *C difficile* infection.

**Methods:** Samples from 633 symptomatic patients were prospectively studied. Each stool sample was tested within 24 hours of receipt in the laboratory in parallel for both the PTAB and GDH immunoassays. When the PTAB and GDH immunoassays were discrepant, a cell culture cytotoxicity assay and the ProGastro™ Cd PCR assay (PG-PCR) to detect DNA from the *tcdB* gene were performed as the gold standard. If there was an additional discrepancy between the cytotoxicity assay and the PG-PCR assay, then direct culture and additional PCR testing (BD GeneOhm™ assay) were used for confirmation.

**Results:** 850 samples were tested, of which 12% were positive for *C difficile* on confirmatory testing. The sensitivity and specificity of the PTAB immunoassay for the detection of *C difficile* were 68% and 98%, respectively. The sensitivity and specificity of the GDH antigen immunoassay for the detection of *C difficile* were 99% and 94%, respectively. The PD-PCR assay was positive in all but 1 confirmed case of *C difficile* infection (1% false-negative rate), and it had 3 false-positive results (2% false-positive rate). The GDH antigen immunoassay combined with molecular testing had the highest sensitivity and specificity and allowed same-day testing and reporting.

**Conclusions:** The Premier *C difficile* Toxin A/B immunoassay lacked sufficient sensitivity for use as a screening test, missing nearly 25% of true-positive samples. PCR was the most sensitive method that also allowed same-day testing and reporting.

**Reviewer's Comments:** Depending on the average laboratory’s workload, combination GDH antigen immunoassay with confirmation molecular testing or molecular testing alone is the strongest performer in detecting *C difficile* infection. Use of the GDH antigen immunoassay alone is not sufficiently specific for use and requires a confirmation test. (Reviewer-Deborah J. Chute, MD).

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**Keywords:** Clostridium difficile, Colitis, Diagnosis.

**Print Tag:** Refer to original journal article
Extra-capsular lymph node extension was an independent predictor of decreased survival in patients with gastric carcinoma, particularly those with N1 disease.

**Background:** Gastric cancer is the second most frequent cause of cancer-related death. One of the most important prognostic factors is lymph node (LN) status. The Japanese Classification of Gastric Carcinoma considers the location of LN metastases relative to the primary tumor, while the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) stage these tumors according to the number of LNs involved by metastasis.

**Objective:** To evaluate the prognostic impact of extracapsular extension by LN metastases in patients with gastric cancer.

**Participants:** 159 patients with gastric carcinoma who underwent either total or subtotal gastrectomy with LN dissection.

**Methods:** The nodal status was classified according to the UICC staging system. Extracapsular LN extension was defined as invasive cancer with penetration through the nodal capsule into perinodal adipose tissue. Deposits of tumor without recognizable LN were also considered extracapsular LN involvement. Additional clinical and pathologic features, including tumor grade and stage, were also recorded. Data were obtained from medical records regarding 5-year survival rates.

**Results:** On average, 37 LNs per patient were examined in each dissection. The number of metastatic LNs was classified as pN0 in 40% of patients, pN1 in 27%, pN2 in 16%, and pN3 in 17%. Of all patients with LN metastases, 60% had extracapsular LN extension of tumor. Extracapsular extension was associated with distant metastasis and increasing LN stage. The 5-year overall survival rate was significantly worse in patients with extracapsular LN involvement (13%) than in those with only intracapsular LN metastases (39%). When stratified by nodal stage, extracapsular LN involvement in pN1 disease was associated with significantly worse survival compared to those with pN1 disease confined to the nodes (5-year overall survival rate, 19% vs 52%, respectively). However, extracapsular extension was not a significant predictor of survival in pN2 or pN3 disease. On multivariate analysis, pT category, presence of residual tumor, and extracapsular LN extension remained significant predictors of survival.

**Conclusions:** Extracapsular LN extension in metastatic gastric carcinoma is significantly associated with increased tumor stage and is an independent predictor of decreased survival. This association was particularly striking in the subset of patients with pN1 disease. Future staging systems for gastric carcinoma will likely include extracapsular extension.

**Reviewer’s Comments:** The presence of extracapsular LN extension is a proven independent predictor of survival in other tumor staging systems, including head and neck carcinoma. It is no surprise that it is a powerful predictor in gastric carcinoma as well. Although not currently required by the AJCC staging system, pathologists may want to include this information in subsequent reports for their clinical colleagues. (Reviewer-Deborah J. Chute, MD).

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**Keywords:** Gastric Carcinoma, Extracapsular Lymph Node Involvement, Prognosis

**Print Tag:** Refer to original journal article
Background: Because the proven benefit of kidney transplantation is proven for patients with end-stage renal disease, there has been an attempt to expand the number of available donor kidneys using organs from older donors (age ≥60 years) or from donors after cardiac death (DCD). However, when no restriction criteria based on histological findings are applied to this new population of donor kidneys, unacceptable rates of graft function and survival are usually observed. Recently, it has been shown that careful selection of potential graft kidneys using results of the Pirani scoring system can successfully differentiate older grafts associated with satisfactory versus unacceptable clinical outcomes.

Objectives: To determine the reproducibility among pathologists of the Pirani scoring system to assess pretransplant kidney grafts, and to determine if estimates of glomerulosclerosis observed on biopsy are representative of the whole kidney.

Methods: Renal biopsy specimens with cortical tissue from DCDs between 1994 and 2005 were reviewed (44 cases). Transplant recipients were followed up until January 1, 2008, or until death. One kidney biopsy was taken from a normal-appearing area at the time of organ recovery or reperfusion. The biopsies were routinely processed and scored independently by 3 pathologists using the Pirani system, which includes semiquantitative scoring (0 to 3) based on the number of globally sclerosed glomeruli, the degree of vascular narrowing, and the degree of tubular atrophy and interstitial fibrosis. After a 6-month interval, 1 pathologist re-scored all cases. Interobserver and intraobserver agreement statistics were calculated. Two core biopsies and 1 large cortical wedge biopsy were also taken from the kidneys of 20 patients who underwent autopsy at the authors’ institution. The number of total and sclerosed glomeruli was counted in each section to assess the precision of estimates of glomerulosclerosis in the core samples.

Results: Interobserver agreement using the standard Pirani system was 0.38. Agreement increased significantly (to 0.64) when a combined measure of tubular atrophy and interstitial fibrosis was used instead (tubular atrophy score/interstitial fibrosis score). The precision of glomerulosclerosis estimates from core biopsies increased with increasing sample size. The limits of agreement were approximately 10% when at least 17 glomeruli were present in the core biopsy tissue.

Conclusions: Histological assessment of pretransplant biopsies from older DCD patients shows adequate reproducibility among pathologists after combining tubular atrophy and interstitial fibrosis measures into a single score. Furthermore, core biopsies taken from the renal cortex provide reasonably precise estimates of global glomerulosclerosis if at least 7 glomeruli are present.

Reviewer’s Comments: Acceptable interobserver agreement is essential when using a scoring system. The results of this study show that a modified Pirani system is useful in assessing donor kidney biopsies for transplant suitability. (Reviewer-T. David Bourne, MD).

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Keywords: Kidney Transplant Biopsy Review

Print Tag: Refer to original journal article
Serum Proteins Can't Take the Heat

Proteomic Analysis of the Effect of Storage Temperature on Human Serum.

Lee DH, Kim JW, et al:


Increasing storage temperatures for human serum are associated with significant protein alterations. The optimal temperature for storing human serum to conserve various proteins is -80°C.

**Background:** Proteomics is a general term referring to the large-scale study of protein identification, expression, structure, and function. Such analysis relies heavily on biochemical techniques, including 2-dimensional polyacrylamide gel electrophoresis (2-DE), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), mass spectroscopy (MS), and ProteinChip® Array analysis, among others. The tools of proteomics currently play essential roles in many translational research studies designed to discover and develop biomarkers for a host of human diseases. As with all tests within the clinical laboratory, many variables may affect the results of protein analysis, including specimen collection method, specimen type, specimen temperature, and analytical method.

**Objectives:** To determine the effects of storage temperature on serum protein samples using various proteomic techniques.

**Methods:** 20 blood samples were collected by venipuncture from 20 volunteers (10 men and 10 women) who had no history of acute or chronic illness. The blood was drawn into serum separation tubes (SST; Becton-Dickenson) and allowed to clot for 1 hour at 4°C. The clot was removed using centrifugation (3000 x g for 15 minutes), and the resulting serum was divided into 4 aliquots and stored at different temperatures: -80°C, -20°C, 4°C, and room temperature (22-24°C). After at least 7 days, samples were analyzed for various high- and low-molecular-weight proteins using SDS-PAGE, 2-DE, and MS techniques, among others.

**Results:** Analysis using 2-DE showed that numerous protein spots showed a significant change after high-temperature storage. These proteins included α2-macroglobulin, C3, and C4, among others. SDS-PAGE showed that some protein bands had significantly different intensities after storage at higher temperatures. ProteinChip Array analysis also showed significant alterations after higher-temperature storage.

**Conclusions:** Serum storage temperature has significant effects on subsequent protein analysis by a number of proteomic methods. Optimal conservation of protein occurs in samples stored at -80°C.

**Reviewer's Comments:** The results of this study from the Korea National Institute of Health do not seem too surprising. However, they underscore the importance of standardizing important pre-analytical factors as much as possible, especially for biomarker assays. Since increasing numbers of esoteric referral tests are now available and requested, the practical importance of basic issues, such as proper specimen storage temperature, cannot be overemphasized. (Reviewer-T. David Bourne, MD).

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Keywords: Human Serum, Storage Temperature

Print Tag: Refer to original journal article
Outcome Favorable for Ovarian Mets From Cervical AIS

Endocervical Adenocarcinoma In Situ With Ovarian Metastases: A Unique Variant With Potential for Long-Term Survival.
Chang MC, Nevadunsky NS, et al:

Int J Gynecol Pathol 2010; 29 (January): 88-92

Extensive endocervical adenocarcinoma in situ without apparent invasion may be associated with ovarian metastases that may have a favorable prognosis.

Endocervical adenocarcinoma in situ (AIS) is associated with high-risk human papillomavirus (HPV), such as HPV16 and HPV18. AIS can extensively affect the endocervix and occasionally extend into the endometrium, but by definition, has not invaded any underlying stroma. Recently, a small series of synchronous endocervical and ovarian tumors were presented, and few were considered metastases from an apparently noninvasive endocervical carcinoma to the ovary. Additional cases of minimally or noninvasive carcinomas simulating primary ovarian tumors were subsequently presented in support.

Objective: To present case reports of endocervical AIS with ovarian metastases. Case 1: A 34-year-old pregnant woman was found to have atypical glandular cells on screening Pap test, AIS on colposcopic biopsy, and extensive AIS involving the margin on cervical conization. Three months after delivery, a hysterectomy was performed to find residual AIS but no invasive disease. Interoperative assessment described normal-appearing ovaries. However, within the next year, an ultrasound detected a 10.5-cm complex pelvic mass that was subsequently excised. The mass was first interpreted as a low-grade (borderline-like) endometrioid adenocarcinoma, but comparison found it to be cytomorphologically similar to the prior AIS. HPV testing showed HPV16 in both lesions. The patient underwent chemotherapy and was alive without disease at the 13-year follow-up. Case 2: A 30-year-old woman was found to have neoplastic glandular cells on screening Pap test and AIS with negative margins on cervical conization. She presented with recurrent AIS several years later for which she had 2 sequential conizations to achieve negative margins. Cervical stenosis compromised further screening, and she underwent a hysterectomy which showed extensive AIS involving the endocervix and endometrium. Invasion was not noted, but a subsequent salpingectomy found a right ovary with an attached 1.8-cm multicystic nodule of invasive adenocarcinoma having similar cytomorphologic features to the AIS. HPV testing showed both lesions to contain HPV16. After chemoradiation therapy, she was alive and well at 9 months.

Conclusions: In cases of extensive or recurrent endocervical AIS, ovarian metastases may be present in the absence of documented stromal invasion. Although only 8 cases have been presented in the literature, this context may confer a favorable prognosis.

Reviewer’s Comments: We may rarely, if ever, encounter this scenario, but recognizing the possibility may prevent the misdiagnosis of a synchronous ovarian carcinoma. HPV testing provides a reliable marker for distinguishing between the 2 lesions. (Reviewer-Mary T. Galgano, MD).

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Keywords: Endocervical Adenocarcinoma, Ovarian Metastases, Survival

Print Tag: Refer to original journal article
Features associated with response to tyrosine kinase inhibitors in lung adenocarcinomas include hobnail cells and BAC or micropapillary patterns. These are more common in young nonsmoking women of East Asian descent.

Background: Epidermal growth factor receptor (EGFR) is a tyrosine kinase (TK) protein expressed on many normal cells, playing a role in proliferation and differentiation. Overexpression of EGFR due to mutations or other alterations has been related to carcinogenesis as well as invasive and metastatic potential of such carcinomas. Understanding this role of EGFR has lead to targeted therapy using TK inhibitors (TKIs) such as gefitinib and cetuximab. These agents have been used in selected carcinomas shown to have mutations in the EGFR gene, particularly including non-small cell lung cancer (NSCLC).

Objective: To review the current published literature on correlating EGFR mutation status with clinicopathologic features of NSCLC, specifically focusing on cell type and pattern.

Results: EGFR mutations appear to be prevalent in young, female, nonsmokers of East Asian ethnicity. Histopathologic features first noted to be associated with response to EGFR TK inhibitors and mutations of EGFR include bronchioloalveolar carcinoma (BAC) subtype and other well to moderately differentiated adenocarcinomas. More recently, hobnail cell type (in contrast to columnar or polygonal cell type) has been found to be associated with a statistically significant higher incidence of EGFR mutations. This cell type is described as having cytoplasmic protrusions with a tadpole or hobnail appearance and low p53 expression. In addition, the micropapillary pattern (MMP) has been recently associated with mutations in EGFR. This pattern is described as having papillary structures or tufts but lacking a true fibrovascular core, and while associated with nonsmokers, it has an aggressive clinical course even when matched for stage.

Conclusions: EGFR TKIs can provide effective treatment options for patients with NSCLC. However, patients found to have mutations or alterations in the EGFR gene are most likely to respond. Clinicopathologic features associated with response to targeted therapy and/or a detected EGFR mutation include young, female, nonsmokers of East Asian descent and hobnail cytology with BAC or MMP histology.

Reviewer’s Comments: These findings provide features we can use for surveying tumors that may benefit from molecular testing for EGFR mutations, or presumptive therapy with TKIs. (Reviewer-Mary T. Galgano, MD).

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Keywords: Lung Cancer, EGFR Status, Effect on Clinicopathologic Features

Print Tag: Refer to original journal article
LLL Clonal B-Cell Population Not Predictive of Lymphoma

Florid Reactive Lymphoid Hyperplasia of the Lower Female Genital Tract (Lymphoma-Like Lesion): A Benign Condition That Frequently Harbors Clonal Immunoglobulin Heavy Chain Gene Rearrangements.

Geyer JT, Ferry JA, et al:

Am J Surg Pathol 2010; 34 (February): 161-168

Some lymphoma-like lesions of the lower female genital tract show clonal B-cell proliferation. However, the presence of IgH rearrangement does not correlate with clinical outcome.

Background: True lymphomas of the lower female genital tract are very uncommon, whereas inflammatory lesions resembling lymphoma are seen “not infrequently.” In the mid-1980s, lymphoma-like lesions (LLLs) of the lower female genital tract were described. These lesions most often involve the cervix but can be seen throughout the tract. They are most frequently seen in women of reproductive age. LLLs are characterized by a dense superficial inflammatory infiltrate often with admixed large atypical lymphoid cells. No cases of LLL have been found to evolve to lymphoma, although occasional cases have been reported with concomitant viral infections.

Objective: To document a series of LLLs with particular attention to clonal rearrangements of immunoglobulin heavy chain (IgH).

Methods: A computer search was conducted for patients diagnosed with LLLs at a single hospital during a 9-year study interval. Clinical and follow-up data were obtained. Immunohistochemistry (IHC) was performed with antibodies to numerous lymphoid antigens. PCR was performed, and cases were assessed for IgH rearrangements.

Results: There were 12 cases, and patients ranged in age from 18 to 54 years. Of these cases, 9 involved the cervix (most often seen with loop electrosurgical excision procedure specimens), and 3 involved the endometrium. Most cervical lesions presented in patients being worked up for cervical dysplasia. With the cervical cases, a dense superficial band-like infiltrate was present. Ulceration was present in 7 cases, and 3 cases had follicular hyperplasia. IHC staining identified active lymphoid follicles. Four cases had a more diffuse infiltrate. Large and small lymphocytes were present, admixed with plasma cells and neutrophils. Epstein-Barr virus was identified in 2 cases. Two cases also showed a slight predominance of B cells. With the 3 endometrial cases, all had features of chronic endometritis. Four of the 7 cervical cases showed clonal receptor rearrangements. The histology did not appear different between the cases with clonal receptor rearrangements and those without them. Lymphoma did not develop in any patient.

Conclusions: Lymphoma-like lesions of the female genital tract can sometimes show clonal receptor rearrangements. Nonetheless, they behave in a benign fashion.

Reviewer’s Comments: Pathologists should be aware that not all apparently clonal LLLs of the female lower genital tract are malignant. Interestingly, many of the cases seen in this study were originally diagnosed as lymphomas. (Reviewer-Edward B. Stelow, MD).

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Keywords: Florid Reactive Lymphoid Hyperplasia, Lymphoma-Like Lesions

Print Tag: Refer to original journal article
Ionizing radiation is a risk factor for papillary microcarcinoma of the thyroid.

**Background:** The incidence of papillary microcarcinomas (PMCs) of the thyroid (papillary thyroid carcinomas <1 cm in size) has been increasing. These tumors usually show benign behavior, but occasional metastases have been reported. Thus, the optimal treatment of PMCs is associated with some controversy. Furthermore, the relationship between these tumors and ionizing radiation is unclear, although ionizing radiation is a known risk factor for conventional papillary thyroid carcinomas.

**Objective:** To investigate the clinicopathologic features of a series of PMCs of the thyroid seen in patients exposed to atomic bomb radiation.

**Methods:** A cohort of patients surviving the atomic bomb blasts of Hiroshima and Nagasaki was used. PMCs were identified within the cohort of nearly 8000 patients who had either surgical or autopsy material available. Pathological materials were reviewed. PMCs were considered those papillary thyroid carcinomas <1 cm in greatest dimension. Results were compared to radiation dose estimates.

**Results:** 458 PMCs were identified in 313 patients. This translated to a prevalence of 4.5% at the time of death. Approximately 75% of patients had only 1 tumor. Overall, women represented two times more cases than did men. More than 75% of patients were aged >60 years at the time of their deaths. Of the tumors evaluated, 75% were nonencapsulated and sclerosing, whereas only 3% were considered follicular variants of papillary thyroid carcinoma. About 25% of the tumors were <1 mm in size. Radiation dose was significantly associated with the presence and number of PMCs, and this did not appear to be age-dependent.

**Conclusions:** Exposure to ionizing radiation increases one’s risk for the development of PMCs of the thyroid in a dose-dependent fashion.

**Reviewer's Comments:** Although the increased detection of PMCs in this study appears to be secondary to radiation exposure, it is difficult to know how this relates to the overall increased rate of these tumors in patients today. It still seems likely that some of the increased incidence of these lesions is secondary to changes in diagnostic criteria, especially in the United States. (Reviewer-Edward B. Stelow, MD).

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Keywords: Papillary Microcarcinoma, Ionizing Radiation vs Risk

Print Tag: Refer to original journal article