Liver biopsies in patients with chronic viral hepatitis represent a useful screening tool for other liver diseases.

**Background:** Although there is an emergence of noninvasive methods to stage liver biopsies in patients with chronic hepatitis, biopsy remains the gold standard. Additionally, these biopsies serve as a valuable screening tool to assess for other underlying pathology.

**Objective:** To assess a large series of liver biopsies from patients with chronic hepatitis for the presence of other, nonviral related pathologies.

**Methods:** Between July 2001 and June 2007, a total of 1,842 consecutive liver biopsies from patients with chronic hepatitis (HBV or HCV) were reviewed.

**Results:** In 377 patients (20.5%), 410 other diagnoses were identified. The most common diagnoses included steatosis (>10%; 135 cases), followed by steatohepatitis (116 cases), hemosiderosis (62 cases), hepatocellular carcinoma (HCC) (58 cases), dysplastic nodule (16 cases), and granulomas (7 cases). Other less frequent diagnoses include drug-induced hepatitis, primary biliary cirrhosis, Wilson's disease, metastases, cholangiocarcinoma, chronic lymphocytic leukemia, alpha-1-antitrypsin deficiency, cystic fibrosis, and schistosomiasis. **Discussion:** Some of these findings are associated with chronic viral hepatitis, such as HCC and steatosis. However, steatosis should still be correlated with other risk factors. In 4 of the 7 cases with granulomas, further work-up revealed 2 cases of tuberculosis and 2 cases of sarcoidosis. In 2 patients, the necroinflammatory activity was greater than that expected given the low HBV titers of the patients. Further clinical work-up and screening identified drugs and herbal treatments as the underlying etiology. Most of the hemosiderosis cases were secondary (SH), likely due to mutations in the HFE gene, however there were 7 cases of primary hemosiderosis (PH). The authors note that there is no reliable parameter to distinguish PH from SH, and clinical correlation is required in all cases. Wilson's disease was diagnosed in 2 patients as the degree of fibrosis was too advanced for the viral load and the age of the patients. **Conclusions:** The authors identified other processes in almost 25% of the liver biopsies in patients with chronic hepatitis. Some of these processes have the potential to modify disease progression or patient management.

**Reviewer's Comments:** This is a clinically useful study that carefully reviews other pathologies we might encounter while reviewing liver biopsies in patients with chronic hepatitis. Once a liver is cirrhotic, it is difficult to assess for other pathologies, which is why these pre-cirrhotic biopsies are useful screening tools in these patients. (Reviewer-William A. Kanner, MD).

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Keywords: Chronic Viral Hepatitis, Liver Biopsy, Staging

Print Tag: Refer to original journal article
Touch imprint cytology and frozen section analysis have similar sensitivities and specificities in the diagnosis of metastatic breast carcinoma involving SLNs.

**Background:** One of the most important prognostic factors for breast carcinoma is axillary lymph node status. The sentinel lymph node (SLN) biopsy is a minimally invasive procedure that can help spare some patients from the morbidity of a complete nodal dissection. Many surgeons now request intraoperative evaluation of SLNs so the axillary dissection can be performed during the same procedure if needed. The most common intraoperative techniques for evaluation of SLNs are touch imprint cytology and frozen section.

**Objective:** To evaluate the sensitivity and specificity of cytology and frozen section to detect breast cancer metastasis in SLN biopsies.

**Methods:** 40 patients with T1/T2 breast cancer and clinically negative nodes, who were undergoing axillary lymph node dissection along with mastectomy, were included in the study. Patients with multifocal disease, preoperative chemotherapy, and locally advanced disease were excluded from the study. SLNs were bisected along the long axis, and 4 imprint smears (2 hematoxylin and eosin [H&E], 2 May-Grunwald-Giemsa) were made from each cut surface. Then a portion of each SLN was submitted for frozen section; if the initial H&E frozen section was negative, additional sections were taken. Rapid immunohistochemistry was performed in negative cases using a cytokeratin stain (taking approximately 25 minutes) on the third frozen section level. The remaining lymph node was paraffin embedded for final histopathologic examination, which was considered the gold standard. Tumor deposits were classified as either macrometastases (>2 mm) or micrometastases (>0.2 mm to 2 mm).

**Results:** Imprint cytology was positive for metastatic carcinoma in 22 cases (55%), and frozen section was positive for metastatic carcinoma in 23 cases (57%). In 4 cases, the initial frozen section slide was negative for tumor, and metastatic disease was found on additional levels. Of the metastatic tumor deposits, 17 were macrometastases and 6 were micrometastases. Rapid immunohistochemistry detected only 1 additional case of metastatic tumor cells for which both imprint cytology and frozen section were negative. Final pathologic examination demonstrated metastatic disease in 24 cases (60%). The sensitivity and specificity for imprint cytology were 92% and 100%, respectively; for frozen section, the sensitivity and specificity were 96% and 100%, respectively.

**Conclusions:** Imprint cytology and frozen section evaluation show similar sensitivity and specificity in the detection of metastatic breast carcinoma in SLN biopsies. The addition of rapid immunohistochemistry showed marginal improvement on frozen section evaluation.

**Reviewer's Comments:** Having used both touch imprint cytology and frozen section for the evaluation of SLNs, I have observed results similar to this study. Touch imprint cytology has a lower sensitivity, particularly when not performed as thoroughly as in this paper, but preserves tissue for final pathologic evaluation. (Reviewer-Deborah J. Chute, MD).

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Keywords: Sentinel Lymph Node, Breast Carcinoma, Imprint Cytology, Frozen Section

Print Tag: Refer to original journal article
Intravascular lymphocytosis is a potential mimic of a low-grade lymphoproliferative neoplasm in appendectomy specimens.

**Background:** Most appendectomy specimens are either removed for clinically suspected appendicitis or as an incidental prophylactic procedure as part of another surgery. The authors make the point that in some appendix specimens removed for acute appendicitis, there are prominent intravascular accumulations of monomorphic small lymphocytes. Occasionally, these accumulations may be extensive enough to prompt consideration of a low-grade lymphoproliferative disorder, such as chronic lymphocytic leukemia (CLL).

**Objectives:** To examine the morphologic features, frequency, and associated clinical findings in appendix specimens with prominent intravascular lymphocytosis (IVL).

**Methods:** The authors retrieved 100 appendectomy specimens from 50 men and 50 women. The specimens were removed for a preoperative diagnosis of acute appendicitis; 25 cases within each of the gender groups showed evidence of perforation. Twenty additional cases served as control specimens; these consisted of incidental appendectomy specimens from 10 men and 10 women that were part of larger hemicolectomy specimens removed for colonic adenocarcinoma. All cases with appendiceal neoplasms, inflammatory bowel disease, or infectious colitis were excluded. Slides from each case were reviewed, and the presence or absence of IVL and whether or not a CLL mimic was present was recorded. For the study, IVL was defined as monomorphic lymphocytes completely filling at least 3 separate vascular spaces in any location within the tissue. So-called "exuberant" IVL was defined as at least 3 separate involved vascular spaces within the mesoappendix. For these exuberant cases, the tissue was stained using CD3, CD5, CD10, CD20, and CD23. Clinical and demographic information was also recorded.

**Results:** Approximately 60% of appendicitis cases had IVL compared to only about 15% of the control appendices. Among 26 cases of "exuberant" IVL, 6 were considered so exuberant as to mimic CLL. None of the control group cases showed exuberant IVL. By immunohistochemistry, there was thought to be no definitive evidence for a diagnosis of CLL. Cases of IVL were more frequent in laparoscopic appendectomy specimens and in patients <38 years of age. After at least 2 years of follow-up, no case with IVL has been associated with the development of lymphoma.

**Conclusions:** It is important to recognize the presence of IVL in appendectomy specimens, and to recognize that this finding is a potential mimic of a neoplastic intravascular lymphoproliferative process.

**Reviewer's Comments:** It is interesting that IVL was more commonly found in younger adults, a demographic for which the development of CLL would be very unusual. Gene rearrangement studies would have been useful adjuncts to the immunohistochemical analysis. (Reviewer-T. David Bourne, MD).

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Keywords: Intravascular Lymphocytosis, Acute Appendicitis, Lymphocytic Leukemia

Print Tag: Refer to original journal article
Endometrial Carcinoma in Young Women

Endometrial Carcinomas in Women Aged 40 Years and Younger: Tumors Associated With Loss of DNA Mismatch Repair Proteins Comprise a Distinct Clinicopathologic Subset.

Garg K, Shih K, et al:


Endometrial carcinomas that develop in young women frequently show loss of mismatch repair proteins by immunohistochemistry.

Background: Endometrial carcinomas (ECs) occur predominately in older women. Those that occur in younger women frequently arise in patients with abnormally high estrogen levels, such as women with obesity or polycystic ovarian disease or who are nulliparous. Up to 34% of tumors of young women who develop EC have microsatellite instability (MSI), and germline mutations of mismatch repair (MMR) protein genes occur in approximately one-third of these cases. Because these women may wish to remain fertile, some are treated with conservative therapy. It is furthermore unclear which patients need oophorectomy after hysterectomy.

Objective: This study reviewed the MMR status of ECs in women ≤40 years old and their clinicopathologic features.

Methods: A single institution's database was searched for all cases of EC carcinoma from women ≤40 years of age. All slides were reviewed, and tumors were classified as per the World Health Organization and graded. Numerous histologic features were noted. Immunohistochemistry was performed with antibodies to MLH1, MSH2, MSH6, and PMS2. Only cases with complete absence of tumor staining were considered negative. Immunohistochemistry was performed with antibodies to estrogen receptor (ER) and progesterone receptor (PR). Clinical information was obtained.

Results: Of 2000 hysterectomies for EC, 70 were from women aged ≤40 years of age. The median age was 37 years, and the youngest patient was 24 years of age. Nearly 50% of the women had been obese; 75% were nulliparous and almost 25% were infertile. Less than 10% of patients had polycystic ovarian disease (PCOD) and nearly 10% had a family or personal history of cancer. Seventy-four percent of patients had stage 1 disease, 15% had stage 2, and 10% had stage 3. Ninety-two percent of tumors were endometrioid and, of these, >80% were grade 1 or 2. Five cases had an undifferentiated or dedifferentiated phenotype. Four cases were associated with atypical polypoid adenomyomas. Nine patients had synchronous ovarian carcinomas, 7 of which were endometrioid. Sixteen percent of patients showed loss of MMR protein by immunohistochemistry. These tumors occurred in patients with stronger family histories of cancer and were higher grade and more likely to be undifferentiated. Furthermore, these tumors presented at a higher stage and were more likely to cause death. Finally, tumors with MMR protein loss had significantly less ER and PR immunoreactivity.

Conclusions: The authors note that young women with ECs that show loss of MMR protein by immunohistochemistry fare worse, and should, perhaps, not be considered eligible for conservative therapy.

Reviewer's Comments: Pathologists frequently study colon carcinomas with immunohistochemistry to MMR proteins. It may be helpful to test also ECs that occur in young patients. (Reviewer-Edward B. Stelow, MD).

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Keywords: Endometrial Carcinoma, Younger Age, Microsatellite Instability, Mismatch Repair Protein

Print Tag: Refer to original journal article
The p16-Rb pathway may play a role in MMTT carcinogenesis since many of them stain for p16 in both the epithelial and mesenchymal components.

**Background:** The p16-Rb pathway of cell cycle regulators is over-expressed in HPV-related cervical cancers by functional inactivation of pRB by viral oncoproteins causing a negative feedback on the p16 promoter. Expression of p16 can sometimes be utilized as a marker of HPV-related disease, but many other carcinomas are associated with alterations in this pathway, including endometrial carcinomas. Expression of p16 is especially common in uterine papillary serous carcinoma (UPSC), but even clear cell and high-grade endometrioid carcinomas can be strongly p16 positive. In fact, p16 has been noted to be more intense and diffuse than p53 in UPSC and has been proposed as a differentiator between type I and type II endometrial carcinomas. Limited reports have noted p16 staining in malignant mixed mullerian tumors (MMMTs).**Objective:** To characterize expression of p16 and p53 in the carcinomatous and sarcomatous components of MMMT.**Methods:** 30 MMMTs were collected from the archived files of a single academic institution and reviewed for block selection. Immunohistochemistry for p16 and p53 was performed and scored with a semiquantitative system including both distribution and intensity. Cytoplasmic staining in the absence of nuclear staining was disregarded.**Results:** The epithelial component was UPSC in 33%, endometrioid (FIGO grade 2 or 3) in 63%, and adenosquamous in 1 case. The sarcomatous component was heterologous in 47%, homologous in 43%, and pleomorphic undifferentiated sarcoma in 10%. Expression of p16 was 3+ or 4+ in 60% of the type I (endometrioid and adenosquamous) and 100% of the type II (UPSC) carcinomatous components. Expression of p53 was 3+ or 4+ in 35% of type I and 70% of type II carcinomatous components. Within the type II carcinomatous components, expression of p16 was significantly higher than p53, but within type I, there was no difference in expression. Expression of p16 was 3+ or 4+ in 62% of the homologous and 79% of the heterologous components. Expression of p53 was 3+ or 4+ in 46% and 50% of these components, respectively. The undifferentiated sarcomas were 3+ or 4+ for both. Expression of p16 and p53 were concordant between the 2 components in 90% and 87%, respectively.**Conclusions:** MMMTs express strong and diffuse p16, even more frequently than p53, in both the carcinomatous and sarcomatous components.**Reviewer’s Comments:** The consistent expression of p16 in both components of MMMTs may indicate that the p16-Rb pathway has a role in tumor development. (Reviewer-Mary T. Galgano, MD).
Collagenous Sprue and Celiac Disease


Vakiani E, Arguelles-Grande C, et al:

Mod Pathol 2010; 23 (January): 12-26

Collagenous sprue, defined here as an average basement membrane thickening of ≥5 µm throughout a small bowel biopsy is likely due to celiac disease and may respond to a gluten-free diet alone.

Background: Collagenous sprue may be a nonspecific feature of various diseases, including celiac disease, tropical sprue, common variable immunodeficiency, paraneoplastic syndrome, and others. Regardless of the etiology, it is generally thought to indicate a poor prognosis from severe morbidity and mortality. Few reports have described a good response to therapy, but since there are no well-defined histologic criteria for the amount of collagen deposition, this may be due to diagnostic variability.

Objective: To characterize the clinicopathologic features of collagenous sprue to an objective histologic assessment of collagen deposition.

Methods: The archived files from 2 academic hospitals were searched for small bowel biopsies having increased subepithelial collagen deposition. Two additional groups were also collected for controls, including one without small bowel pathology (normal controls) and another with untreated celiac disease (celiac controls) with subtotal or total villous atrophy. The clinicopathologic data were collected and histologic features documented. Immunohistochemistry was performed to characterize lymphocytic infiltration and polymerase chain reaction to characterize clonality.

Results: By trichrome stain, the subepithelial collagen in normal controls was a discontinuous thin layer (<1.5 µm). Forty percent of the celiac controls were similar, while the other 60% had minimal fibrosis up to 5 µm. Thus, the criteria for collagenous sprue was set at mild (>5 µm to 10 µm), moderate (>10 µm to 20 µm) and marked (>20 µm) fibrosis. Almost all of the collagenous sprue cases had a patchy distribution of collagen with variability in thickness. Seventeen of 19 (89%) of the patients had a diagnosis of celiac disease, with 50% considered refractory. The other 2 were unclassified sprue. None had an infiltrate with an atypical lymphocyte phenotype, and only 1 refractory sprue case was monoclonal. Eight cases responded to a gluten-free diet, and 10 responded to immunomodulatory therapy. One patient died of complications from refractory celiac disease.

Conclusions: Most patients with collagenous sprue have celiac disease, some of whom will respond to a gluten-free diet while others require immunomodulation therapy.

Reviewer's Comments: Collagenous sprue was noted mostly in patients with celiac disease, but only approximately 3% of all celiac disease patients biopsied during the retrospective study period had collagenous sprue. (Reviewer-Stacey E. Mills, MD).

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Keywords: Collagenous Sprue, Prognosis, Celiac Disease

Print Tag: Refer to original journal article
Background: Plasma units are transfused to provide coagulation factors. Fresh-frozen plasma (FFP) is whole blood-derived (WBD) or plasmapheresis-derived (PPD), and plasma frozen within 24 hours after collection (FP24) is also WBD. Thawed FFP and FP24 have a 24-hour shelf life at 1°C to 6°C. Thawed plasma (TP) extends the shelf life to 96 hours beyond the post-thaw 24-hour shelf life. Although not Food and Drug Administration approved, TP is permitted so long as the service is following its own established standard operating procedures (SOP). FP24 and FFP contain hemostatic levels of coagulation factors, and in-vitro studies have also shown hemostatic levels of coagulation factors with TP.  

Objective: To institute a TP SOP in a large academic center and to evaluate its effect on plasma utilization and costs.

Design: After a hospital-wide TP orientation, eligible FFP and FP24 units were identified. PPD units collected from an open apheresis system are not permitted to be converted to TP, and the identification number on these PPD units does not distinguish between a closed or open system, thus PPD FFP units were not eligible. The identified units were converted to TP, discarded, or sold for further manufacture of noninjectible products. Careful clerical check work was also performed. The data, including product utilization and expenses, were then recorded for 1 year prior and 1 year after the protocol was instituted.

Results: Although plasma utilization increased by over 4000 units during the second year, discarded plasma declined from 37 to 13 units after instituting the TP SOP. Plasma wastage and discard declined almost 80% and 65%, respectively, with a cost saving of over $15,000. Approximately 98% of the 193 units followed during this time were transfused within 72 hours of their original thaw date. No clinician inquiries/concerns have been raised, and the hematology physicians have not preferentially requested FFP.

Conclusions: The authors note that FFP, FP24, and TP may be used equivalently for patients who are bleeding or at risk for bleeding secondary to deficiency or dysfunction of coagulation factors for which there is not a factor concentrate available. Utilization of TP offers potential decreased wastage and increased cost savings.

Reviewer's Comments: This article addresses one of the priorities of a transfusion service, which is management of the limited blood supply. It is likely that a TP SOP will become an accepted practice in the future that will lead to better plasma utilization and more cost savings. (Reviewer-William A. Kanner, MD).

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Keywords: Plasma, Blood Utilization, Costs, Thawed Plasma

Print Tag: Refer to original journal article
Cytology alone is less accurate in the diagnosis of hematopoietic malignancy involving the CSF than flow cytometry.

**Background:** Cytologic examination of cerebrospinal fluid (CSF) is valuable in the detection of primary or metastatic lesions involving the central nervous system (CNS). Over 20% of metastatic lesions to the CNS are of hematopoietic origin. Evaluation of CSF for hematopoietic malignancies is difficult due to significant morphologic overlap between reactive and malignant processes. Flow cytometry has greatly enhanced the detection of hematopoietic malignancies involving the CSF, with a reported increase in accuracy of up to 75%.

**Objective:** To evaluate the sensitivity of cytology alone compared to cytology with flow cytometry in distinguishing benign from malignant hematopoietic proliferations in CSF.

**Methods:** 32 consecutive cases of CSF with satisfactory cytology and flow cytometry data over a 5-year period were studied. The original diagnosis, made in the context of clinical history and flow cytometric data, was considered the gold standard. Each case was blinded and independently reviewed by 4 study participants: 1 hematopathologist, 2 cytopathologists, and 1 cytotechnologist. Clinical history and flow cytometry information were not provided to the blinded participants. Each participant categorized the CSF samples as benign or malignant.

**Results:** 16 cases were originally classified as reactive (transverse myelitis, neurosarcoidosis, tuberculosis meningitis, AIDS dementia, or encephalitis), none of which had a history of prior malignancy. Sixteen cases were originally classified as malignant (mantle cell lymphoma, chronic lymphocytic lymphoma, low grade B-cell lymphoma NOS, low-grade T-cell lymphoma, acute myeloid leukemia, large cell lymphoma, or Burkitt lymphoma), 11 of which had a history of hematopoietic malignancy. The overall sensitivity, specificity, positive predictive value, and negative predictive value of cytology alone for CSF evaluation were 52%, 73%, 60%, and 66%, respectively. Cytology alone was more accurate in benign CSF than in malignant CSF specimens (73% accurate vs 52% accurate). Morphologic features that supported a malignant diagnosis were cellular monotony and nuclear membrane irregularities. There was no significant difference in accurate diagnosis of low-grade versus high-grade hematopoietic malignancies.

**Conclusions:** The diagnosis of hematopoietic malignancy on CSF specimens by morphology alone is difficult. Ancillary studies, such as flow cytometry, greatly improve separation of a benign pleocytosis from involvement by lymphoma/leukemia.

**Reviewer’s Comments:** CSF cytology remains indispensable in cases where non-hematopoietic lesions are present. In addition, morphology can be useful in eliminating the presence of peripheral blood contamination of CSF samples, which would lead to a false-positive diagnosis. However, cytopathologists should have a low threshold to triage CSF specimens for flow cytometry in the setting of increased lymphoid or immature myeloid cells. (Reviewer-Deborah J. Chute, MD).

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Keywords: Lymphoma, Leukemia, Pleiocytosis, Cerebrospinal Fluid, Cytopathology

Print Tag: Refer to original journal article
IDH mutational testing may help in the diagnosis, classification, and prognosis of glioma cases.

Background: Isocitrate dehydrogenase (IDH) enzymes 1 and 2 normally catalyze the conversion of isocitrate to alpha-ketoglutarate. IDH1 catalyzes this reaction within peroxisomes, while IDH2 functions within mitochondria. Recently, IDH mutations have been identified in a significant percentage of gliomas, namely diffuse astrocytomas and oligodendrogliomas. The most common mutation involves IDH1 and results from a single amino acid substitution at codon 132 of exon 4 (R132H). Although such mutations have rarely been identified in non-central nervous system (CNS) tumors, these particular IDH mutations seem relatively specific for gliomas. Studies have also shown that IDH mutation status may carry useful prognostic value, since the presence of IDH1 mutations may be associated with prolonged survival compared with grade-matched non-mutated glioma cases.

Objectives: To report a simple and accurate molecular assay to detect the most common IDH1/IDH2 mutations in formalin-fixed, paraffin embedded (FFPE) brain tissue samples and to report the diagnostic use and reliability of this assay.

Methods: 132 FFPE tissue samples from 75 neoplastic and 57 non-neoplastic cases were collected. All tumor cases were reviewed to ensure accurate classification according to current World Health Organization tumor classification criteria (2007). The non-neoplastic specimens included tissues with viral infection, radiation change, and gliosis among others. Unstained tissue sections were manually microdissected to obtain tumor or lesional tissue targets for IDH1 mutation analysis; samples were then submitted for DNA isolation, amplification, and sequencing.

Results: IDH mutations were observed in 37 (49%) of the tumor cases, all of which were from glioma specimens. In 3 of 4 tumor cases obtained using stereotactic biopsy in which the initial biopsy specimen was non-diagnostic, IDH mutations were observed. In total, 97% of the mutations found in tumor samples involved the IDH1 gene, while only 1% of the mutations were detected in the IDH2 gene. No mutations were detected in non-tumor tissue. The detection sensitivity of the assay was 100 viable nuclei from a manually microdissected specimen and at least 20% IDH mutant alleles in a background of normals.

Conclusions: Molecular testing for IDH1 and IDH2 mutations is effective using FFPE brain tissue, and the results may provide additional diagnostic and/or prognostic information not attainable using light microscopic evaluation alone.

Reviewer's Comments: The importance of IDH1/2 mutation analysis in glioma specimens is becoming increasingly recognized. From a practical standpoint, the single fact that such testing can potentially help distinguish reactive (non-neoplastic) brain tissue from neoplastic glial tissue is of singular importance. Anyone who signs out neuropathology cases should follow the IDH story closely. (Reviewer-T. David Bourne, MD).

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Keywords: IDH Mutational Status, Glioma Tissues, Molecular Testing

Print Tag: Refer to original journal article
Lymph node involvement with ovarian serous tumors of low malignant potential is common.

**Background:** It is not uncommon for lymph nodes to be involved with ovarian serous tumors of low malignant potential (OSTLMP) or serous borderline tumors. The finding has been reported in up to 42% of cases. It is unclear, however, whether involvement changes the overall prognosis, and conflicting results have been reported. It is thus also unclear whether women with OSTLMP require lymphadenectomy.

**Objective:** To report the pathologic findings of a larger series of OSTLMP with lymph node involvement.

**Methods:** The surgical pathology files of a single institution were searched for all cases of OSTLMP. A matched control group without lymph node involvement was also retrieved. Tumors were classified as per the World Health Organization and staged. Lymph node lesions more consistent with endosalpingiosis or low-grade serous carcinomas were excluded. Clinical information was obtained.

**Results:** Of the 272 cases of OSTLMP, nearly 25% had lymph node involvement, and of these, 36 cases had available material for review. Patients were of similar age and had similar numbers of lymph nodes sampled. Pelvic lymph nodes were the most frequent lymph nodes involved. Lymph node sizes did not differ between the study and control groups. Tumor within lymph nodes ranged to 2.5 mm in size, and larger lesions showed cystic dilatation of the glandular lesions. A slightly higher percentage of patients in the study group received chemotherapy. The case group was more likely to have invasive implants. Aside then from stage, there were no other pathologic differences between the 2 groups. No unique histologic pattern of lymph node involvement could be identified that correlated with other progressive disease. Patients with lymph node involvement fared worse, however, there was no impact on overall and disease-specific survival when the tumors were compared stage for stage. The size of lymph node involvement and histologic features did not correlate with disease recurrence.

**Conclusions:** Lymph node involvement with OSTLMP is common, and thus, patients with these tumors require lymphadenectomy for proper staging.

**Reviewer’s Comments:** Pathologists should not consider OSTLMP or serous borderline tumors benign. Careful attention should be given to the histologic assessment of lymph nodes from these patients. (Reviewer-Edward B. Stelow, MD).

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Keywords: Serous Tumor of Low Malignant Potential, Lymph Node, Stage

Print Tag: Refer to original journal article
Expression of c-Myc in soft tissue leiomyosarcomas is an independent prognostic factor in a multivariate analysis.

Background: Leiomyosarcomas (LMSs) have a variable clinical outcome with potential for local recurrence and distant metastases. Current independent predictive factors include histologic grade, size of the tumor, and anatomic location. Approximately 25% of those with intermediate risk will have metastatic disease in 5-year follow-up. Downregulation of the gene integrin alpha 7 has been noted to correlate with aggressive behavior in LMS, and the c-Myc gene has been noted to cause downregulation of this gene. The expression of c-Myc has been described as correlating to poor outcome in other sarcomas, and it may have implications in the prognosis in soft tissue LMS.

Objective: To evaluate the prognostic significance of c-Myc expression in soft tissue LMS.

Methods: LMSs were retrieved and reviewed from archived files to include only those in deep soft tissue (excluding subcutaneous and visceral lesions). Immunohistochemistry for c-Myc was performed and correlated with the clinicopathologic features of each. Positive c-Myc expression was defined as specific staining of >5% of the tumor cell nuclei.

Results: 28 cases of soft tissue LMS were collected, of which 15 (54%) were positive for c-Myc expression. The expression of c-Myc did not correlate with any histopathologic feature. With a median follow-up of 23 months, 12 patients died (43%) and 12 (43%) developed metastatic disease. Three additional patients had metastatic disease at presentation. The median overall survival was 35 months, and the median metastasis-free survival was 23 months. There was a significant decrease found in the metastasis-free survival of patients with c-Myc–positive LMS when compared to the c-Myc–negative LMS patients (P = 0.014). The overall survival was also decreased in those with c-Myc–positive LMS (P = 0.017). High histologic grade also correlated with decreased outcome in a univariate analysis. Multivariate analysis disclosed c-Myc expression as the only statistically significant independent prognostic factor.

Conclusions: Expression of nuclear c-Myc in soft tissue LMS predicts for decreased metastasis-free as well as overall survival independent of other clinicopathologic features.

Reviewer's Comments: The expression of c-Myc in soft tissue LMS appears to add valuable prognostic information independent of the routinely used parameters of grade and stage. (Reviewer—Mary T. Galgano, MD.)

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Keywords: Leiomyosarcoma, Prognostic Factors, cMyc

Print Tag: Refer to original journal article
Management of IBDU Patients Remains Complicated

Rigorous Histopathological Assessment of the Colectomy Specimen in Patients With Inflammatory Bowel Disease Unclassified Does Not Predict Outcome After Ileal Pouch-Anal Anastomosis.

Nasseri Y, Melmed G, et al:
Am J Gastroenterol 2010; 105 (January): 155-161

Rigorous assessment for atypical features of ulcerative colitis of colons removed for irritable bowel disease is not helpful for predicting pouch complications.

**Background:** Patients with ulcerative colitis (UC) who undergo colectomy are frequently given an ileal pouch-anal anastomosis. Patients with Crohn’s disease (CD) generally do not get these due to risks for complications and failure of the pouch. The optimal treatment of patients with unclassified disease (ie, inflammatory bowel disease unclassified [IBDU]) is less clear. Some have advocated rigorous histologic assessment of colectomy specimens prior to making the anastomosis, with the belief that with such assessment, it can be predicted which patients will develop pouch complications.

**Objective:** To investigate the use of specific histologic features in patients undergoing colectomy to predict pouch complications and the development of CD.

**Methods:** Patients undergoing colectomy diagnosed with UC or indeterminate colitis and given an ileal pouch-anal anastomosis were studied. Demographic and clinical information were collected. Colectomy specimens were reviewed for histologic findings atypical for UC, including broad-based ulcer, V-shaped ulcer, slit-like fissure, crypt-associated granuloma, isolated giant cells, true granuloma, discontinuous active inflammation, discontinuous chronic inflammation, transmural inflammation, muscle hypertrophy, neural hypertrophy, ileal villous architectural distortion, ileal ulcer, ileal pyloric metaplasia, backwash ileitis, discontinuous ileitis, and appendiceal involvement. Four features were considered most essential for a diagnosis of indeterminate colitis; these included discontinuous chronic disease, transmural inflammation, V-shaped or fissuring ulcer, and discontinuous ileitis. The development of pouch complications and CD were recorded.

**Results:** There were 153 patients ranging in age from 8 to 78 years. Almost 20% of patients developed acute pouchitis, about 10% developed chronic pouchitis, and 8% developed CD. Almost all patients had at least 1 atypical histopathologic feature for UC, most often broad-based ulcer or appendiceal involvement. Neural hypertrophy was the only feature by univariate analysis to be associated with the development of CD (3 of 13 patients who developed CD had this finding). No other features were associated with an adverse outcome. Patients determined to have indeterminate colitis were not at increased risk for the development of any complications.

**Conclusions:** Management of patients who have IBDU remains complicated. Those found at resection to have CD are not usually treated with an ileal pouch-anal anastomosis. Other than recognizing these patients, pathologists are currently unable to predict which patients who receive an ileal pouch-anal anastomosis will develop complications.

**Reviewer’s Comments:** It certainly remains important for pathologists to distinguish CD from other forms of inflammatory bowel disease at resection. Rigorous assessment for atypical features of ulcerative colitis is likely not necessary. (Reviewer-Erward B. Stelow, MD).

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Keywords: Inflammatory Bowel Disease, Pouchitis, Crohn’s Disease

Print Tag: Refer to original journal article
Adult patients with T-cell ALL have a high complete response rate and half survive 5 years. Poor outcome is associated with complex cytogenetics and blasts that are CD13 positive and CD1a negative.

**Background:** T-cell acute lymphoblastic leukemia (T-cell ALL) in adults is a relatively rare entity, and it has been difficult to evaluate the clinical and biologic factors of this disease. T-cell ALL is more common in children and young adults, and patients typically present with a high leukocyte count. By immunophenotype, cytoplasmic CD3 is most often positive and considered lineage specific. Surface CD7 is also a feature of T-cell ALL.

**Objective:** To review the clinical features, immunophenotype, cytogenetics, and outcome of T-cell ALL in adults from a large, randomized, prospective trial.

**Methods:** T-cell ALL patients were selected from a cohort of 1927 adult patients with ALL registered between 1993 and 2006. Immunophenotyping and flow cytometry study data were collected and reviewed when available. Likewise, cytogenetics, fluorescence in situ hybridization (FISH), and molecular genetic investigations were also reviewed when available. Regarding treatment, all patients between 15 and 59 years of age (although the age requirements changed slightly during later years) received identical 4-drug induction therapy including central nervous system (CNS) prophylaxis and treatment if present. Patients with human leukocyte antigen (HLA)-matched sibling donors received an allograft, while those without a matched donor or over the age limit were randomized to receive either an autologous transplantation or consolidation/maintenance therapy. Before all therapy, patients received 3 doses of high-dose methotrexate and asparaginase. Outcome data were also studied.

**Results:** 356 uniformly treated patients were studied. The overall complete response rate (CR) was 94% and 48% for patients who survived 5 years. Poorer outcomes were associated with older patients (>35 years), females, and in 27% of patients with white blood cell (WBC) counts >100 x 10^9/L. CNS involvement at the time of diagnosis did not seem to affect survival. By immunophenotype, lack of expression of CD1a and expression for CD13 were associated with poorer survival. Observed mutations in tested patients included NOTCH1 (61%) and CDKN2A (42%). Complex cytogenetic abnormalities were associated with worse 5-year survival (19% vs 51%). Regarding outcomes, there was not a difference in 5-year survival between patients who received an autograft or chemotherapy. Patients with a matched sibling donor, however, had a superior 5-year survival (61% vs 46%). Of the 123 patients who relapsed, only 8 survived.

**Conclusions:** This study adds important data to the discussion of the treatment and outcome of adult patients with T-cell ALL.

**Reviewer's Comments:** This is a thorough and comprehensive study of a disease that is beginning to be better understood. Importantly, matched sibling donors are a viable treatment strategy in these patients. As pathologists, we should take note that there are biologic factors that we can assess in the patients that may be associated with worse outcome, namely complex cytogenetics, CD13 positivity, and CD1a negativity. (Reviewer-William A. Kanner, MD).

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Keywords: T-Cell Acute Lymphoblastic Leukemia, Outcome

Print Tag: Refer to original journal article
Chronic immune stimulation underlies chronic lymphocytic leukemia.

**Background:** Chronic lymphocytic leukemia (CLL) is a neoplasm of mature B lymphocytes and is the most common form of leukemia among adults in Western countries. Research has focused on whether there is an immune component that precedes CLL, and it is thought that the leukemia is derived from activated, antigen-experienced B cells. It is unclear if protein abnormalities present before a diagnosis of CLL are triggered by an infectious agent or if they are the result of underlying immune defects.

**Objective:** To review patterns of serum protein abnormalities in patients ultimately diagnosed with CLL.

**Methods:** The authors identified 109 persons who developed CLL and had prediagnostic serum samples stored as a result of the nationwide Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (up to 9.8 years before the diagnosis). The patterns of free light chains (FLCs), M-proteins, and serum protein assays were studied.

**Results:** Of the patients, 38% and 13% had an abnormal FLC ratio and a monoclonal (M)-protein, respectively, >2% to 3% reported in the general population (>50 years old). In all but 1 case, all patients with an involved FLC had the corresponding κ or λ tumor cell immunophenotype or were biclonal, thus supporting that the FLCs and M-proteins seen before a diagnosis of CLL might be by-products of the CLL cell turnover. In 61 patients (who had normal FLC ratios and no M-protein), there were elevated levels of FLC, indicating polyclonal B-cell activation. Only 3% of CLL patients had prediagnostic hypogammaglobulinemia, supporting that this might be a late event in CLL development. Females appear to have a more favorable prognostic disease profile. In this study, only 1 female (compared with 10% of males) had an M-protein before CLL diagnosis.

**Conclusions:** In approximately 40% of patients diagnosed with CLL, the authors found serum evidence of M-protein abnormalities detectable up to 9.8 years before diagnosis. Elevated free κ or λ FLC levels were identified in an additional 16% of patients. These results indicate a role for chronic immune stimulation in the etiology of CLL, and it is suggested that the CLL clone and the observed serum protein abnormalities originate from the same clone.

**Reviewer’s Comments:** CLL is one of the most often diagnosed leukemias that we encounter. This article addresses some of the recent research into this disease, utilizing tests that are readily available. As the authors admit, one weakness of the study is the lack of available blood samples at the time of CLL diagnosis. (Reviewer-William A. Kanner, MD).

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Keywords: CLL, M-Protein, Free Light Chains, Hypogammaglobulinemia

Print Tag: Refer to original journal article
Have 2007 Guidelines for HER2 Testing Had an Effect on HER2 Status?


Shah SS, Ketterling RP, et al:

*Hum Pathol* 2010; 41 (January): 103-106

The 2007 guidelines for evaluating HER2 immunohistochemistry down-scored <3% of all breast carcinoma cases, of which 50% were amplified by FISH.

**Background:** Human epidermal growth factor receptor 2 (HER2) gene amplification is associated with a significantly worse prognosis in patients with breast carcinoma, but can be treated with anti-HER2 therapy. Therefore, accurate assessment of HER2 status is necessary for treatment recommendations in breast cancer patients. In 2007, the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) made new recommendations in an attempt to standardize HER2 testing and improve the accuracy and reproducibility of this test. In particular, the grading of the HER2 immunohistochemical stain (IHC) was changed, with reflex testing to fluorescence in situ hybridization (FISH), if equivocal (2+).

**Objective:** To evaluate the impact of the change in the interpretation of HER2 IHC results and its correlation with FISH testing.

**Methods:** All cases of invasive breast carcinoma with IHC testing for HER2 over a 7-year period were searched. All cases with a score of 3+ according to the HerceptTest guidelines (≥10% cells with medium to strong membrane staining) were included. Of these, 141 cases had available tumor slides and blocks available. The HER2 IHC slides were reviewed, and the results were scored according to the ASCO/CAP 2007 guidelines (2+ if 10% to 30% of cells with moderate membrane staining, 3+ if >30% of cells with strong membrane staining). HER2 amplification by FISH was performed in all cases with 2+ staining, and classified as amplified if the gene ratio was >2.2 or the HER2 gene copy number was >6.

**Results:** Of the 141 cases, 12 (8.5%) would have had HER2 IHC classified as 2+ by the 2007 criteria. Of these 12, 6 were positive for HER2 gene amplification by FISH, 4 were negative, and 2 were equivocal. Interestingly, 1 case showed dramatic intra-tumoral heterogeneity, with high amplification in areas with 3+ IHC staining and no amplification in areas with 1 to 2+ IHC staining.

**Conclusions:** The 2007 ASCO/CAP guidelines down-scored only 2.8% of tumors from positive to equivocal HER2 IHC results, of which 50% had HER2 gene amplification by FISH testing. Additional studies are needed to determine whether the new guidelines are better at predicting response to anti-HER2 therapy.

**Reviewer's Comments:** Most studies have shown good correlation between HER2 IHC and FISH analysis, and this study supports those results. It is important to note that dramatic intra-tumoral heterogeneity for HER2 can be seen, and testing on the resection specimen may be helpful in equivocal cases. (Reviewer-Deborah J. Chute, MD).

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**Keywords:** HER2, FISH, Immunohistochemistry, Breast Carcinoma

**Print Tag:** Refer to original journal article
How Do Locked Nucleic Acids Help With Classifying Fungal Organisms?

In Situ Detection of Aspergillus 18s Ribosomal RNA Sequences Using a Terminally Biotinylated Locked Nucleic Acid (LNA) Probe.

Montone KT, Feldman MD:

Diagn Mol Pathol 2009; 18 (December): 239-242

Locked nucleic acid probes can be used to detect *Aspergillus* spp. in paraffin-embedded tissues, as these probes show high affinity and thermal stability.

**Background:** Speciation of fungal organisms in formalin-fixed paraffin embedded (FFPE) tissue remains a constant problem, particularly in patients who did not have a culture performed. In addition, many cultured fungal organisms cannot be speciated unless the fruiting bodies grow, which is a tedious and labor-intensive process. Therefore, nucleic acid probes to detect specific ribosomal RNA (rRNA) sequences of fungal organisms have been developed. Locked nucleic acids (LNA) are modified nucleotides with an additional methylene group, which hybridize strongly to their complementary RNA and DNA sequences. This creates thermally stable hybrids, allowing the use of significantly shorter probes. These features are optimal for in situ hybridization (ISH) assays.

**Objective:** To report the first development of a LNA probe to identify *Aspergillus* 18s rRNA sequences in FFPE tissues.

**Methods:** 20 specimens with culture-proven *Aspergillus* spp. (including *fumigatus, flavus, niger, and nidulans*) along with 20 culture-proven non-*Aspergillus*-negative fungal controls (*Blastomyces, Candida, Sporothrix, Histoplasma, Scedosporium, Zygomycetes,* and *Fusarium* spp.) were examined. All specimens were FFPE tissue from either surgical or post-mortem samples. A synthetic 23-nucleotide probe was developed using LNA nucleotides to target a sequence of the 18s rRNA of *Aspergillus* spp. In addition, a conventional DNA oligonucleotide probe with the same sequence was synthesized. In situ hybridization was performed with both the LNA and the DNA probes on each sample. All slides were examined by light microscopy to evaluate for positive staining in the target organisms. Intensity of staining was evaluated by measuring the optical density of the chromogen after ISH.

**Results:** All 20 *Aspergillus* spp. showed strong staining with the LNA probe; both hyphal forms and fruiting bodies were highlighted. The DNA oligonucleotide probe also stained all 20 samples, but with overall weaker signal. All negative controls were negative for both the LNA probe and the DNA oligonucleotide probe. On average, the LNA probe demonstrated a signal that was 2.1 times stronger than the DNA probe.

**Conclusions:** ISH with an LNA probe targeting *Aspergillus* 18s rRNA is useful for rapidly detecting *Aspergillus* spp. in paraffin-embedded tissue. In addition, the LNA probe showed a stronger signal than its corresponding DNA probe.

**Reviewer's Comments:** Locked nucleic acids are a new molecular technology that is very promising for ISH assays. The stronger signal will allow detection at lower organism counts, and the shorter probes will allow more versatility in testing design. (Reviewer-Deborah J. Chute, MD).

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Keywords: In Situ Hybridization, Locked Nucleic Acids, Aspergillus, Ribosomal RNA

Print Tag: Refer to original journal article
The presence of a particular single-nucleotide polymorphism in the MMP-12 gene appears to confer improved lung function among adult smokers and asthmatic children.

**Background:** The matrix metalloproteinase 12 (MMP-12) protein, encoded by the MMP12 gene, has been shown to play a role in emphysema development in mice that have received cigarette smoke exposure. This protein is secreted by macrophages, which represent the predominant cell type within the lower air spaces of the lung. Macrophages are also the primary cell type recruited to the air spaces in response to cigarette smoke exposure. When MMP12 expression increases, there is increased elastin degradation, which is also a stimulus for macrophage recruitment. In humans, it has been shown that MMP12 expression increases nearly 10-fold in smokers compared to nonsmokers.

**Objectives:** To test the hypothesis that variants in MMP12 may influence the later development of chronic obstructive pulmonary disease (COPD) in humans.

**Methods:** The association between single-nucleotide polymorphisms (SNPs) in the MMP12 gene and the results of spirometry testing measuring forced expiratory volume in 1 second (FEV1) was determined. The case population included adults and children from 7 patient cohorts representing >8300 test subjects. The cohorts included children with asthma, as well as cohorts of adults with and without COPD. The association between various MMP12 SNPs related to FEV1 and the time to COPD onset was first determined within a cohort of initially healthy adult men. This was followed by examination of the association between various MMP12 SNPs and COPD development in 1 separate adult cohort, one comprised of adults with COPD and the other comprised of adults at risk for COPD development. Survival curve estimates from regression modelling were constructed as part of the statistical analysis.

**Results:** The authors report that a certain SNP in MMP12 (designated rs2276109) is positively associated with better lung function among a cohort of children with asthma and in cohorts of adult patients with COPD or with increased COPD risk. Among adult smokers, the presence of this SNP in MMP12 appeared to confer a decreased risk of COPD. Interestingly, the absence of this particular SNP conferred a 54% increased risk of COPD onset.

**Conclusions:** A particular SNP in MMP12 is associated with positive lung function among adults who smoke and among children with asthma. Among adult smokers, the presence of this SNP appears to confer a reduced risk of COPD development among smokers.

**Reviewer's Comments:** This is an interesting article emphasizing the potentially large contribution that a relatively small molecular alteration may have on disease phenotype. The authors do discuss limitations of the study, including the fact that the findings were not uniformly significant among all individual cohorts. (Reviewer-T. David Bourne, MD).

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Keywords: Lung Disease, Molecular Markers, MMP12, Lung Function, COPD

Print Tag: Refer to original journal article
We May Have a New Marker for High-Grade Lymphomas

Analysis of Aurora B Kinase in Non-Hodgkin Lymphoma.

Ikezoe T, Takeuchi T, et al:

Lab Invest 2009; 89 (December): 1364-1373

Expression of Aurora B in non-Hodgkin lymphoma is strongest in high-grade lymphoma subtypes.

**Background:** The so-called Aurora kinases are members of the serine/threonine kinase family, and they play key roles during the process of mitosis. The 3 members of the Aurora kinase family include kinases A, B, and C. Aurora B is involved in chromosomal alignment and mitotic spindle assembly. Previous research has shown that a number of solid tumors show overexpression of the Aurora A and B kinases. It has also been observed that selective inhibitors of Aurora B may induce growth arrest and apoptosis of various solid malignant tumors.

**Objectives:** To analyze the expression by immunohistochemistry of Aurora B in various subtypes of non-Hodgkin lymphoma (NHL).

**Methods:** 71 paraffin-embedded malignant lymphoma samples were retrieved and submitted for routine immunohistochemistry using an anti-Aurora B antibody (Epitomics). The number of positive cell nuclei was recorded using the following semiquantitative scale: weakly positive (+; >5% to 20%), moderately positive (++; >20% to 80%), and markedly positive (+++; >80%). Various tumor cell lines, including Burkitt lymphoma cells, were obtained in order to culture with a selective Aurora B inhibitor.

**Results:** The high-grade, clinically aggressive NHLs, diffuse large B-cell lymphoma and Burkitt lymphoma (BL), showed strong nuclear expression of Aurora B. In contrast, the lower-grade tumors, including follicular lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, and mantle cell lymphoma, showed only slight Aurora B immunoreactivity. Thus, expression of Aurora B was strongly correlated to histological grade. Aurora B expression also showed a positive correlation with a high International Prognostic Index (IPI) score. Cultured BL cells showed growth arrest upon treatment with a selective Aurora B inhibitor (AZD1152-HQPA).

**Conclusions:** Cases of high-grade B-cell lymphoma, including diffuse large B-cell lymphoma and BL, show high nuclear expression of Aurora B. In contrast, the vast majority of lower-grade B-cell lymphoma subtypes, such as follicular lymphoma, mantle cell lymphoma, and MALT lymphoma, show no to weak positivity. Furthermore, exposing cultured tumor cells (in vitro) to a selective inhibitor of Aurora B results in marked growth arrest and tumor cell apoptosis.

**Reviewer's Comments:** The authors add another tumor type to the growing list of tumors in which the Aurora kinase proteins are overexpressed. Their results have added interest, however, given their additional tissue culture studies demonstrating the effectiveness of a selective Aurora B kinase inhibitor. (Reviewer-T. David Bourne, MD).

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Keywords: High-Grade Lymphoma, Immunohistochemistry, Aurora B Kinase, Non-Hodgkin Lymphoma

Print Tag: Refer to original journal article
Retroperitoneal fibrosis is frequently associated with increased IgG4-immunoreactive plasma cells.

**Background:** Retroperitoneal fibrosis (RF) is an uncommon sclerosing lesion of the retroperitoneum. It can arise in a number of different settings, and some have suggested autoimmune disease as the etiology, especially as some patients may also have sclerosing cholangitis or sialadenitis. As these other lesions are sometimes associated with elevated serum levels of immunoglobulin G4 (IgG4) and increased number of IgG4 plasma cells (IgG4-related disease), it is not surprising that some have speculated that retroperitoneal fibrosis may also be an IgG4-related disease.

**Objective:** To review the clinicopathologic features of a series of cases of RF with particular attention to IgG4 status.

**Methods:** 17 cases of RF were identified from multiple institutions. All cases had a typical lymphoplasmacytic infiltrate with fibrosis and none had neoplasms. Cases were classified as related to IgG4 disease if the number of IgG4 immunoreactive plasma cells exceeded 30% of the total IgG-immunoreactive plasma cells. Clinical and pathologic features were compared between groups of patients.

**Results:** 10 cases were IgG4 related and 7 were not. IgG4-related disease was more likely to be associated with obliterative phlebitis; however, other histologic features were not statistically different between the groups. All patients with IgG4-related disease were men, whereas all but 1 of the non–IgG4-related cases were from women. Serum IgG4 concentration and IgG4 to IgG ratios were significantly higher in patients with IgG4-related disease. Five patients with IgG4-related disease had other sclerosing lesions, while none of the patients with non–IgG4-related lesions had other sclerosing lesions. There was not a statistical difference in response to steroid therapy between the groups of patients.

**Conclusions:** RF is a heterogeneous disease; however, a majority may be secondary to systemic IgG4-related disease. It may be helpful to identify these patients as they are at greater risk for the development of other sclerosing lesions.

**Reviewer's Comments:** The pathology journals continue to publish report manifestations of IgG4-related disease. The disease appears to affect numerous sites throughout the body, including the pancreatobiliary system, salivary glands, lungs, and lymph nodes. (Reviewer-Edward B. Stelow, MD).

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Keywords: Retroperitoneal Fibrosis, IgG4, Plasma cells, Sclerosing

Print Tag: Refer to original journal article
Exposure to formaldehyde increases one’s risk for the development of myeloid leukemia.

**Background:** Formaldehyde exposure is not uncommon within the United States, and >2 million workers have been exposed to the chemical within the last few decades. People working in exposed professions, such as funeral workers and pathologists, have been shown to have increased rates of death from lymphohematopoietic and central nervous system (CNS) malignancies as well as nasopharyngeal carcinomas. Recently, formaldehyde has been listed as a human carcinogen by the International Agency for Research on Cancer (IARC).

**Objective:** To investigate rates of malignancy in the funeral industry.

**Methods:** Previous large studies that identified dead workers from the U.S. funeral industry were used. Death certificates from embalmers and funeral directors were reviewed for causes of death and contributing factors. The study group included all patients dying of lymphohematopoietic, CNS malignancies, and nasopharyngeal malignancies. The control group included persons working in the funeral industry who died of other causes. Next of kin interviews were performed to obtain work practice, demographic, and other social information. A model developed to estimate the formaldehyde exposure based on a number of factors, such as type of formaldehyde, ventilation status, etc, was used.

**Results:** There were 244 control patients and 209 case patients, composed predominately of white males. Tobacco use was common in case and control patients. Embalming was associated with an increased risk for the development of myeloid leukemia (odds ratio, 11). The degree of exposure was also directly correlated with the risk for developing myeloid leukemia. Although embalmers did develop more brain cancers, the results were not statistically significant. Only 4 cases of nasopharyngeal carcinoma were identified within the study and no significant increased risk for this disease was seen in embalmers compared to those who were not exposed to formaldehyde.

**Conclusions:** Exposure to formaldehyde is directly related to the development of myeloid leukemia. Those with high levels of cumulative exposure were at the greatest risk for the development of disease.

**Reviewer's Comments:** This study should be of special interest to us pathologists as many of us are exposed to formaldehyde on a daily basis. Proper ventilation within our grossing stations should be a priority for us. (Reviewer-Edward B. Stelow, MD).

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Keywords: Formalin, Malignancy, Leukemia, Embalmers

Print Tag: Refer to original journal article
Plasmacytoid cells in follicular lymphomas are frequently clonally related, and the distribution of such cells may indicate a separate subtype with features of marginal zone lymphoma.

**Background:** Follicular lymphomas (FLs) recapitulate germinal center cells, but can show maturation into post-follicular cells. Plasma cells and marginal zone differentiation within FLs have been demonstrated to have a clonal relationship in some cases, and FL with marginal zone differentiation may have a distinct cytogenetic profile. Some have proposed that these represent marginal zone lymphomas or composite lymphomas, and this consideration should be explored.

**Objective:** To explore the characteristics of FLs with a plasma cell component for evidence of a unique phenotype.

**Methods:** Fluorescence immunophenotype and interphase cytogenetic analysis of 14 FL with plasmacytic differentiation (identified by CD138) was performed for CD10, BCL2, BCL6, IGH@ and MALT1 break apart probes and a chromosome 12 centromeric probe. CD10, BCL2, and BCL6 were positive in 12/14, 12/14, and 12/12, respectively. Light chain restriction was utilized to characterize the predominant location of the plasma cells. Twelve of 14 cases had a cytogenetic abnormality, and in the 10 evaluable cases, it was identical between the non-plasma cell component and the plasma cell component. Rearrangements were seen in BCL2 (n=7) and BCL6 (n=2), some of which also had IGH rearrangements or +MALT1 without +18. None had Trisomy 3 noted in association with marginal zone lymphoma. Isolated IGH alterations were noted in 2 more cases. A predominance of interfollicular plasma cells was noted in all 6 cases with isolated BCL2 rearrangements, while most of those without a BCL2 alteration had intrafollicular or perifollicular plasma cells.

**Conclusions:** Identical molecular alterations detected in both the lymphoid and plasmacytoid cells of FL support a clonal relationship of many cases. The distribution of the plasmacytoid cells in cases with and without BCL2 rearrangements may indicate a subset that has features overlapping with marginal zone lymphomas.

**Reviewer’s Comments:** In the absence of molecular evaluation, the distribution of plasma cells in a follicular lymphoma may indicate which have features overlapping with a marginal zone lymphoma. (Reviewer-Mary T. Galgano, MD).
Pulmonary Sarcomatoid Carcinoma Are Poorly Differential Tumors


Franks TJ, Galvin JR:

Arch Pathol Lab Med 2010; 134 (January): 49-54

Sarcomatoid carcinomas of the lung are a poorly differentiated NSCLC with 5 major subtypes that should be recognized.

**Background:** Sarcomatoid carcinomas (SCs) of the lung are a subtype of non-small cell lung cancer (NSCLC) that have a variety of subgroups recognized in 2004 by the World Health Organization (WHO); these subtypes include pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. The new WHO classification of SCs reflects the evolving theory of carcinoma with divergent differentiation from totipotential stem cells. The importance in recognizing the different morphologies may be differentiating these lesions from other anaplastic mimics, primary and metastatic to the lung.

**Objective:** To present the published WHO classification of SCs of the lung.

**Results:** SCs present similarly to other smoking-related NSCLCs, except pulmonary blastoma, which has an average age of 35 years at presentation and has an equal sex distribution. Pleomorphic carcinoma is a poorly differentiated non-small cell carcinoma, adenocarcinoma, squamous cell carcinoma, or large cell carcinoma admixed with at least 10% malignant spindle and/or giant cells. The spindle cells vary from epithelioid to spindle and are arranged in fascicular or storiform patterns. Spindle cell carcinoma is a non-small cell carcinoma of only spindle cells. Giant cell carcinoma is a non-small cell carcinoma of only anaplastic, giant cells. Carcinosarcoma is a non-small cell carcinoma admixed with a sarcomatous component, such as malignant cartilage or skeletal muscle. In order of frequency, the carcinomatous component is squamous, adenocarcinoma, adenosquamous, and least commonly, large cell carcinoma. The sarcomatous component is most frequently rhabdomyosarcoma, osteosarcoma mixed with chondrosarcoma, and then osteosarcoma alone. Pulmonary blastoma consists of a primitive epithelial, fetal-type adenocarcinoma admixed with a primitive mesenchymal stroma sometimes with rhabdomyosarcomatous, osteosarcomatous, or chondrosarcomatous components. Tumors should be submitted with 1 section per centimeter despite the sometimes large size. Broad spectrum keratins can be employed, but are not necessary in the presence of conventional carcinomatous components. Spindle cell carcinoma may be difficult to distinguish from a primary sarcoma, although the former is considered more common than the latter. Synovial sarcoma is a common primary and metastatic sarcoma that can sometimes be distinguished by the characteristic t(X;18). Malignant mesothelioma may also be difficult to exclude with immunohistochemistry, but correlation with clinical and radiographic features may be contributory.

**Conclusions:** Sarcomatoid carcinomas of the lung are a heterogeneous and poorly differentiated group of tumors that should be recognized to avoid misclassification.

**Reviewer's Comments:** Small tissue biopsies may make classification difficult, but recognition of these subtypes can lead to a reasonable differential diagnosis, which should be combined with clinical and radiographic information. (Reviewer-Mary T. Galgano, MD).

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Keywords: Sarcomatoid Carcinoma, Lung, Histologic Criteria, Lesions

Print Tag: Refer to original journal article