

CTCs Predict Chemotherapy Resistance in Breast Cancer

Cytokeratin-19 mRNA-Positive Circulating Tumor Cells After Adjuvant Chemotherapy in Patients With Early Breast Cancer.

Xenidis N, Ignatiadis M, et al:
J Clin Oncol; 27 (May 1): 2177-2184

Circulating tumor cells in the blood of breast cancer patients, as indicated by RT-PCR detection of CK-19 mRNA, independently predict chemotherapy resistance.

Background: There is growing interest in the laboratory detection of circulating tumor cells (CTCs) as surrogate markers for response to cancer chemotherapy, specifically breast, prostate, colon, and lung carcinomas. A single FDA-approved method (CellSearch) uses antibody-coated magnetic beads and semiautomated fluorescent microscopy. Investigators at Massachusetts General Hospital (MGH) are developing a different immunoaffinity method, which uses a microfluidic chip containing antibody-coated "microposts." The University of Southern California and the California Institute of Technology (USC/Cal Tech) are developing a completely different microfilter system, which is predicated on larger CTC size.

Objective: To assess whether RT-PCR detection of cytokeratin-19(CK-19)-positive CTCs predicts chemotherapy response in women with breast cancer.

Method: RNA was extracted from peripheral blood specimens from 437 breast cancer patients (stage I to stage III) at 3 different times: before chemotherapy, 3 to 4 weeks postoperatively, and 3 to 4 weeks after completion of chemotherapy. Real-time RT-PCR was performed using primers for CK-19 (Stathopoulou A, Gizi A, et al: *Clin Cancer Res* 2003;9:5145-5151) and products were normalized to a cultured human mammary carcinoma cell line, MCF-7. Median follow-up was 53.5 months (range, 10-106 months).

Results: In a previous study, 2 of 89 (2.2%) normal females demonstrated >0.6 MCF-7 cell equivalents per 5 micrograms of total RNA, the threshold for positivity. In this study, 179 of 437 breast cancer patients (41.0%) were positive for CTCs prior to chemotherapy. Following chemotherapy, CK-19 mRNA-positive cells were demonstrated in 143 (32.7%). Positivity for CK-19 mRNA was associated with having 4 or more positive lymph nodes but not with any other clinicopathologic feature. Fifty-six patients converted from CK-19 mRNA-negative to positive and 92 patients converted from CK-19 mRNA-positive to negative following chemotherapy. The presence of detectable CK-19 mRNA either before or after chemotherapy independently predicted unfavorable disease-free and overall survival by multivariate analysis.

Conclusion: RT-PCR demonstration of CK-19 mRNA in the blood of breast cancer patients independently predicts chemotherapy resistance.

Reviewer's Comments: In a previous comparison of methods for detecting CTCs, RT-PCR was a more sensitive method than cellular filtration or immunomagnetic separation (Ring AE, Zabaglo L, et al: *Br J Cancer* 2005;92:906-912). However, in that comparison, the exact cellular filtration and immunomagnetic separation methods were not identical to those that are now used in the FDA-approved CellSearch system, the MGH microfluidic chip, or the USC/Cal Tech microfilter system. The practical application of CTCs is evolving. The optimal method, ideal cutoff threshold, and clinical utility remain unproven.

Additional Keywords: Circulating Tumor Cells

print tag: () Refer to original journal article.

Proliferative Grading Stratifies Patients With Parotid AciCC

Clinical and Pathologic Prognostic Features in Acinic Cell Carcinoma of the Parotid Gland.

Gomez DR, Katabi N, et al:

Cancer; 115 (May 15): 2128-2137

High-grade acinic cell carcinomas of the parotid gland are more likely to be associated with local recurrence, metastasis, and death than are low-grade tumors.

Background: Acinic cell carcinoma (AciCC) is a rare malignancy of the major salivary glands, representing <10% of all salivary gland tumors. Although typically less aggressive than other salivary gland malignancies, a subset of AciCC behave in a malignant manner. Surgery is the treatment of choice, but indications for adjuvant or postoperative therapy have not been established.

Objective: To examine a single institution's experience with AciCC and to evaluate these cases for clinical and pathologic predictors of outcome.

Participants: 35 patients treated at 1 institution for AciCC of the parotid gland, with treatment and follow-up data available.

Methods: Clinical features recorded included age, gender, performance score, presentation, and extracapsular extension (ECE) identified at surgery. Pathologic features recorded included tumor size, presence of lymph node metastasis, mitotic activity, necrosis, tumor grade, histologic ECE, lymphovascular and perineural invasion, and margin status. Tumors were graded as high-grade when mitotic activity was >2/10 high power fields and/or tumor necrosis was present. Low-grade tumors lacked both features. All patients were treated by surgical excision, with or without lymph node dissection and radiotherapy. The 5-year estimates of disease free survival (DFS) and overall survival (OS) were calculated.

Results: The median follow-up time was 60 months. Five patients (14%) failed during follow-up (local failure only, n=1; locoregional failure and distant metastasis, n=2; distant metastasis only, n=2). Two patients died of disease. The 5-year DFS and OS were 85% and 90%, respectively. On univariate analysis, the following features were significantly associated with worse DFS and/or OS: clinical ECE requiring nerve sacrifice; lymph node involvement at diagnosis; high mitotic activity; tumor necrosis; and positive surgical margins. High-grade tumor histology was present in 7 patients, including all 5 who failed after surgery. The DFS and OS were 94% and 100%, respectively, for low-grade tumors and were 54% and 69%, respectively, for high-grade tumors.

Conclusion: Although AciCC of the parotid is considered a less aggressive salivary gland tumor, a significant subset will fail treatment, and half of these patients will die of disease. A histologic grading system identified all cases that failed in this series. This grading system may allow some low-risk patients to avoid the morbidity of additional therapy.

Reviewer's Comments: This is the largest study to date on AciCC from a single institution with uniform treatment recommendations. Additional studies with multivariate analysis are needed to determine if the histologic grading system proposed in this article remains an independent predictor of survival.

Additional Keywords: Acinic Cell Carcinoma

print tag: () Refer to original journal article.

Urachal Carcinomas Frequently Recur, Metastasize

Urachal Carcinoma: A Clinicopathologic Analysis of 24 Cases With Outcome Correlation.

Gopalan A, Sharp DS, et al:

Am J Surg Pathol; 33 (May): 659-668

Urachal carcinomas typically present at high stage and often behave poorly.

Background: Urachal carcinomas represent <1% of all bladder carcinomas. They are believed to develop from the urachus, a vestigial structure that connects the bladder and allantois during embryonic development and later becomes the urachal ligament. Occasional entrapped epithelial elements may be present (urachal remnants), and these can develop into cysts and neoplasms, usually involving the anterior dome of the bladder. The neoplasms are most often epithelial and develop out of glandular metaplasia, hence most have an intestinal phenotype.

Objective: To examine the clinicopathologic features of a large series of adenocarcinomas of the bladder dome.

Methods: 67 tumors on the bladder dome were identified from the surgical pathology files of a single institution. Twenty-four cases were best classified as urachal carcinomas (tumor located in dome or anterior wall; tumor epicenter was in bladder wall; absence of widespread cystitis cystica or glandularis; and absence of other known primary tumor.) Clinical and follow-up information were pursued. All histologic materials were reviewed. Immunohistochemistry was performed with antibodies to a number of different antigens.

Results: Tumors were from 15 men and 9 women with a mean age of 52 years. Patients received partial cystectomy or extended partial resection, with resection of the umbilicus in most cases. Uncommonly, patients received adjuvant chemotherapy or radiation therapy. Most tumors demonstrated local extension beyond the urachus into the bladder or abdominal wall (pT3). Thirteen tumors were classified as adenocarcinomas, not otherwise specified, and 9 had enteric differentiation. Urachal remnants were identified in 15 cases, and cystitis cystica or glandularis was identified in 4 cases. By immunohistochemistry, all tumors were reactive with antibodies to CK20 and CDX2. Most were immunoreactive with antibodies to 34BE12, and approximately half were immunoreactive with antibodies to CK7. Only 1 of 15 cases tested showed nuclear localization with antibodies to beta -catenin. At a mean follow-up of 43 months, nearly a third of cases had recurred. Metastases occurred with 9 patients, mostly to regional lymph nodes or the lungs. Nearly a third of patients died of disease, usually after developing both regional recurrence and metastases.

Conclusions: Most urachal carcinomas present at higher stage and frequently develop local recurrence and metastases. The immunohistochemical findings are similar to colorectal adenocarcinomas, except that they frequently are immunoreactive with antibodies to 34BE12.

Reviewer's Comments: This is a large series of urachal carcinomas for which strict definitions were applied for classification. The postulation that the tumors seed the lower tract may explain the recurrence rate but also brings into question the classification of some of the primary tumors.

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Serum CRP & IL-6 Not Elevated in IgG-4 Related Disease

Systemic IgG4-Related Lymphadenopathy: A Clinical and Pathologic Comparison to Multicentric Castleman's Disease.

Sato Y, Kojima M, et al:

Mod Pathol; 22 (April): 589-599

IgG4-related disease should be considered in cases of systemic lymphadenopathy with prominent plasma cells.

Background: IgG4-related diseases, including autoimmune pancreatitis, sclerosing sialadenitis, retroperitoneal fibrosis, and sclerosing cholangitis, have been noted to involve regional and systemic lymph nodes. However, this facet of the disease has not been carefully characterized. The clinical presentation may overlap with that of multicentric Castleman's disease, given the somewhat nonspecific systemic manifestations. The histologic appearance also overlaps, with both disease processes having a prominent plasma cell infiltration, but a comparison of the 2 has not been performed.

Objective: To evaluate the clinicopathologic features of patients with IgG4-related lymphadenopathy.

Methods: Nine patients with IgG4-related lymphadenopathy were identified. All were diagnosed by elevated serum IgG4 (>135 mg/dL) and lymph nodes with infiltrating plasma cells (IgG4/IgG-positive cell ratio >40%).

Clinicopathologic information was collected and reviewed. Immunohistochemistry was performed for CD20, CD3, CD5, CD10, CD21, CD138, Bcl-2, IgG, IgG4, Kappa, Lambda, and human herpes virus type-8 (HHV8). PCR was performed for detecting the immunoglobulin heavy chain gene (IGH) and T-cell receptor (TCR) gamma gene rearrangement.

Results: 7 men and 2 women with a median age of 72 years (range, 45-82 years) were identified as having systemic lymphadenopathy with a clinical or histologic suspicion of multicentric Castleman's disease and/or lymphoma. All cases were negative for HHV8, and none was clonal by PCR. The cases had 2 histologic appearances: an interfollicular plasmacytosis and an intra-germinal center plasmacytosis. The interfollicular type had either Castleman's disease-like features or an atypical lymphoplasmacytic and immunoblastic proliferation-like features. The intra-germinal center type had prominent follicular hyperplasia with germinal center infiltration of IgG4-positive plasma cells, some reminiscent of progressive transformation of germinal centers. Eight of the 9 cases also had lymph node infiltration by eosinophils, and examined patients also had elevated serum IgE. Elevated serum IgG4 levels were part of the diagnostic inclusion criteria, but all patients also had elevated soluble interleukin-2 receptors, and 4 of 5 patients tested were found to have autoantibodies. In contrast, interleukin-6, CRP, and LDH were normal or only minimally elevated in all but 1 patient.

Conclusions: IgG4-related lymphadenopathy is associated with an interfollicular or intra-germinal center infiltration of IgG4-positive plasma cells and increased serum IgG4 levels. In contrast to multicentric Castleman's disease, these patients tend to have normal serum CRP and interleukin-6 levels.

Reviewer's Comments: The lymphadenopathy and hypergammaglobulinemia of IgG4-related disease may overlap clinically with multicentric Castleman's disease, but the authors describe serum tests that may aid in the differential diagnosis of these systemic diseases.

Additional Keywords: IgG4-Related

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Elevated Leptin May Be Marker of Salivary Gland Tumors

Salivary Leptin as a Candidate Diagnostic Marker in Salivary Gland Tumors.

Schapher M, Wendler O, et al:

Clin Chem; 55 (May): 914-922

Determination of leptin concentration in saliva may help discriminate patients with salivary gland tumors from healthy individuals.

Background: Various substances such as steroids, amines, and other peptides are found in human saliva, and salivary concentrations of these substances are highly correlated to plasma concentrations. Leptin is a relatively recently investigated cytokine that was initially found to play a role in the regulation of food intake and energy expenditure. Leptins also may play a role in tumorigenesis and tumor metastasis. In normal salivary glands, leptins and leptin receptors are expressed within acini and intralobular duct cells. Leptins have also been identified within the saliva of healthy individuals.

Objective: To characterize the expression of leptin and its receptors in various salivary gland tumors.

Methods: Normal parotid gland tissue from 31 patients undergoing surgery for indications other than tumors and parotid tumor tissue from 97 patients undergoing tumor resection were studied. Portions from each fresh tissue sample were formalin-fixed, stored in RNAlater solution, or flash frozen. One day before surgery, saliva samples were collected from 77 patients with salivary gland tumors. Saliva samples were also collected from a group of 22 healthy individuals and from a small number of patients with salivary gland enlargement secondary to stones or cysts. Groups were matched for gender, age, and body mass index. Tumor types included pleomorphic adenoma, adenolymphoma, basal cell adenoma, and various carcinomas. Samples were analyzed using immunohistochemistry (IHC), immunofluorescence, immunoblotting, and quantitative real-time PCR. Primary antibodies for IHC and Western blot analysis included rabbit polyclonal antibodies to human leptin and goat polyclonal antibodies against the leptin receptor. ELISA was used to measure salivary and plasma leptin concentrations.

Results: Leptin expression was significantly higher among salivary gland tumors compared to healthy parotid tissue. By IHC, all tumor types showed intense, predominantly cytoplasmic, staining for leptin in at least 95% of tumor cells. In nonneoplastic parotid tissue, leptin expression was present within intercalated, striated, and intralobular ducts and in basal portions of glandular acini. Tumors also overexpressed leptin receptor isoforms. Measured leptin concentrations in saliva from patients with tumors of any type were significantly higher compared to control values.

Conclusions: Determination of leptin concentration in whole saliva may prove to be a useful diagnostic marker of salivary gland neoplasia in contrast to other causes of salivary gland enlargement, such as gland lithiasis or cyst formation. Its ability to discriminate among various tumor types requires additional study.

Reviewer's Comments: The utility of determining leptin expression by IHC seems limited, since both benign and malignant salivary gland neoplasms show strong expression of the leptin protein. Detecting subclinical disease, however, would be useful.

Additional Keywords: Diagnostic Markers

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EBV Often Present in Lung Carcinomas With LEL Morphology

Epstein-Barr Virus-Associated Adenocarcinomas and Squamous-Cell Lung Carcinomas.

Gomez-Roman JJ, Martinez MN, et al:

Mod Pathol; 22 (April): 530-537

Lymphoepithelioma-like morphology is rare in pulmonary carcinomas, but when present may be associated with the Epstein-Barr virus.

Background: As many as 90% of lung cancers are associated with cigarette smoking. However, other environmental agents have also been implicated, such as asbestos, radon, and silica. The Epstein-Barr virus (EBV) is closely linked to several malignancies, particularly undifferentiated carcinoma of the nasopharynx, which is also known as lymphoepithelioma. The World Health Organization has described a pulmonary neoplasm in the large-cell carcinoma category as lymphoepithelioma-like carcinoma (LEL). This is characterized as having the typical syncytial growth pattern of undifferentiated neoplastic cells with vesicular nuclei and prominent nucleoli, shown to be associated with EBV in Asian populations. However, rare pulmonary carcinomas without the LEL morphology have also been shown to be associated with EBV.

Objective: To determine the incidence of EBV in pulmonary carcinomas with a dense lymphoid background in a Western population.

Methods: All pulmonary non-small cell carcinomas surgically treated at a single hospital in Spain were reviewed for a prominent lymphoid infiltrate and indistinct tumor-stromal interface (features shared with lymphoid neoplasms). In addition, 70 conventional pulmonary squamous cell carcinomas and adenocarcinomas were reviewed. Tissue microarrays were constructed and subjected to EBER1/EBER2 in situ hybridization (EBER ISH) and LMP1 immunostaining. A subset was also analyzed for viral sequences by PCR methods.

Results: 19 of 1,545 pulmonary carcinomas (1%) had the LEL appearance. Of these cases, 6 had focal areas of squamous differentiation (intercellular bridges or keratinization), 8 had areas of glandular differentiation (tubuloglandular pattern and mucin production), and 5 had neither. Ten cases were positive for EBER and PCR, but only 3 of the 10 were positive for LMP1. This included 4 of the 6 cases with squamous differentiation and 6 of the 8 cases with glandular differentiation, but none with a pure LEL morphology. EBER was positive in 2 additional adenocarcinomas, but these were negative by PCR and LMP1. All PCR- and/or EBER-negative cases were also negative for LMP1. The conventional pulmonary carcinomas were not positive for EBV by any method of detection.

Conclusions: A small subset of pulmonary carcinomas in a Western population have features of lymphoepithelioma-like carcinomas and may contain EBV DNA or RNA sequences.

Reviewer's Comments: The authors found evidence of EBV in 12 of 19 pulmonary carcinomas with LEL-like morphology in a Spanish hospital.

Additional Keywords: Epstein-Barr Virus

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GUCY2C in Lymph Nodes Prognostic for pN0 Colorectal Cancer

Association of GUCY2C Expression in Lymph Nodes With Time to Recurrence and Disease-Free Survival in pN0 Colorectal Cancer.

Waldman SA, Hyslop T, et al:
JAMA; 301 (February 18): 745-752

GUCY2C expression identifies node-negative colorectal cancer patients who are at increased risk for early recurrence, even though the majority of GUCY2C-positive patients do not recur.

Background: Lymph node status is the most powerful prognostic indicator in colorectal cancer. Recurrence is seen in 50% of stage III patients (node-positive, no distant metastases) and in 25% of stage II patients (node-negative, muscle invasion), suggesting occult node metastases may be missed by conventional methods of pathologic examination in stage II patients. Guanylyl cyclase 2C (GUCY2C) is a candidate molecular marker of metastatic potential in colorectal cancer.

Objective: To evaluate a quantitative RT-PCR assay for GUCY2C gene expression as a predictor of occult colorectal cancer lymph node metastases and patient survival.

Methods: 2,570 fresh lymph nodes >5 mm were obtained from 273 patients with node-negative (stage 0 to II) and 87 patients with node-positive (stage III) colorectal cancer from 9 hospitals in the United States and Canada. Nodes were bisected, and half of each was fresh-frozen for quantitative RT-PCR analysis of GUCY2C gene expression while the other half was formalin-fixed for histology. Median clinical follow-up was 24 months (range 2-63 months).

Results: Among 32 pN0 patients with GUCY2C-negative lymph nodes, 30 remained disease-free (recurrence rate, 6.3%). In contrast, among 225 pN0 patients with GUCY2C-positive lymph nodes, 47 experienced recurrence (recurrence rate, 20.9%). Occult molecular metastasis (pN0, GUCY2C-positive) was associated with reduced disease-free survival. In patients with pN0 colorectal cancer, the following factors were not highly prognostic: tumor grade, anatomic location, lymphovascular invasion, and number of lymph nodes. In contrast, detection of GUCY2C in lymph nodes from pN0 patients was a significant, independent prognostic indicator.

Conclusions: Molecular staging by quantitative RT-PCR for GUCY2C expression identifies node-negative colorectal cancer patients who are at increased risk for early recurrence and poor survival.

Reviewer's Comments: These authors carefully emphasize that positive nodal status, detected either by conventional or molecular pathologic methods, is not a certain predictor of disease recurrence. Most node-negative colorectal cancer patients do not experience recurrent disease, even though 87.5% have molecular evidence of GUCY2C expression. The real clinical utility of this or similar work will be realized when a molecular assay is proven to predict which stage II colorectal cancer patients will benefit from adjuvant chemotherapy.

Additional Keywords: Prognosis

print tag: () Refer to original journal article.

Mucin Stains Not Reliable for Differentiating Pseudocysts

Pseudocyst of the Pancreas: The Role of Cytology and Special Stains for Mucin.

Obeso EG, Murphy E, et al:

Cancer Cytopathol; 117 (April 25): 101-107

Special stains for mucin did not reliably distinguish pancreatic pseudocysts from neoplastic mucinous cysts.

Background: The incidental detection of asymptomatic pancreatic cysts has been increasing due to the use of high-resolution cross-sectional imaging techniques. Although most of these cysts are benign, those with an underlying malignancy have a dismal prognosis. Currently, imaging and cyst fluid analysis are the primary tools used to distinguish benign from malignant pancreatic cysts. Pseudocysts are reported to represent >90% of all pancreatic cysts, but little information is available on the cytomorphologic features of these lesions.

Objective: To report the authors' experience with pseudocysts and to compare the cytomorphologic features with those of neoplastic mucinous cysts (NMCs).

Methods: 42 patients underwent endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) of a pancreatic cyst, which was eventually diagnosed as pseudocyst. Radiology findings, cyst fluid analysis (amylase and carcinoembryonic antigen [CEA] levels), and EUS findings were recorded. Papanicolaou-stained aspirate slides were evaluated for background mucin, inflammatory cells, pigment, and fat necrosis. Alcian blue and mucicarmine stains were performed on each case to evaluate the presence of extracellular mucin. The cytomorphologic features of an additional 110 FNA cases of histologically confirmed NMCs (intraductal papillary mucinous neoplasm, or mucinous cystic neoplasm) were included for comparison.

Results: On CT and EUS, a diagnosis of pseudocyst was made in 85% and 69% of patients, respectively. Forty patients (95%) had a prior diagnosis of pancreatitis. Cyst fluid CEA levels were available on 21 patients, of which 85% were <100 ng/mL. Cyst fluid amylase was >250 IU/mL in all patients. A minimal amount (1+) of extracellular mucin was identified in 4 pseudocysts; no cases had 2+ or greater mucin. Either acute inflammation or abundant histiocytes were found in 75% of cases. Fat necrosis and extracellular pigment were present in 24% and 31% of samples, respectively. Three cases (7%) had atypical epithelial cell clusters. Alcian blue stains and mucicarmine stains were positive for extracellular mucin in 64% and 40% of cases, respectively. In comparison, NMCs had fluid CEA levels >192 ng/mL in 60% of cases, abundant extracellular mucin (2-3+) in 29% of cases, and limited extracellular mucin (1+) in an additional 21% of cases. Alcian blue and mucicarmine stains were positive for mucin in 57% and 38% of NMCs, respectively.

Conclusion: The diagnosis of pancreatic pseudocyst depended primarily on imaging findings and cyst fluid analysis. The cytologic features were frequently nonspecific. Special stains for mucin did not reliably distinguish pseudocysts from NMCs.

Reviewer's Comments: While the presence of limited mucin (1+) was nonspecific, the finding of abundant, thick, extracellular mucin easily appreciated on Papanicolaou stain virtually excludes pancreatic pseudocyst.

Additional Keywords: Diagnosis

print tag: () Refer to original journal article.

Two Novel Types of Pediatric Liposarcomas Identified

Liposarcomas in Young Patients: A Study of 82 Cases Occurring in Patients Younger Than 22 Years of Age.

Alaggio R, Coffin CM, et al:

Am J Surg Pathol; 33 (May): 645-658

Most pediatric liposarcomas are myxoid liposarcomas. However, 2 novel types were identified in this population, a myxoid type with spindled cells and a myxoid type with pleomorphic cells.

Background: Liposarcomas represent a little more than 10% of the soft tissue malignancies seen in adults. However, liposarcomas are very rare in children and comprise <3% of soft tissue malignancies in these patients.

Objective: To review a large series of liposarcomas seen in patients between the ages of 5 and 22 years. Clinicopathologic features and genetic changes were assessed.

Methods: All liposarcomas previously diagnosed in patients between 5 and 22 years old at multiple institutions during a nearly 20-year study interval were reviewed. Any cases believed to be wrongly classified were excluded. Clinical and follow-up information were recorded. Cases were classified as per the World Health Organization classification system for soft tissue tumors and graded. The FUS, CHOP, EWSR1, and MDM2 gene loci were evaluated using split-apart FISH.

Results: 82 cases were reviewed from 28 males and 54 females (mean age, 15.4 years). Approximately half the cases occurred in the thigh or leg, and the remaining cases occurred widely distributed throughout the body. Tumors ranged from 3 cm to 17 cm in size. A median follow-up of 59 months was available for about 70% of the cases. Slightly more than 70% of tumors were considered to be conventional myxoid/round cell liposarcomas, most of which were grade 1 of 3. Ninety-four percent of patients were alive and free of disease after complete resection. Only 3 patients developed recurrences, and none developed metastases. Six cases were myxoid but had >25% spindle cell growth. Two of 4 patients developed recurrences, and 1 developed a metastasis. Twelve cases were myxoid but also had admixed areas of pleomorphic liposarcoma. Nearly half of these tumors were present in the mediastinum. Seven of 10 patients with these tumors died of their disease. There were only 4 cases of well-differentiated liposarcoma/dedifferentiated liposarcoma and 2 cases of conventional pleomorphic liposarcoma. FUS-CHOP and EWSR1-CHOP rearrangements were only seen in conventional myxoid liposarcomas. There was no amplification of the MDM2 gene seen in any case. Higher tumor grade was associated with worse outcome.

Conclusions: Most pediatric liposarcomas are myxoid liposarcomas. Two novel types of liposarcomas were identified in this population, a myxoid type with spindled cells and a myxoid type with pleomorphic cells.

Reviewer's Comments: In this well-written manuscript, the authors discuss a large series of pediatric liposarcomas. It will be interesting to see if the possible variants of myxoid liposarcoma that they describe remain classified as such, given the lack of genetic mutations.

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No Diagnostic Immunostain for Urothelial Micropapillary Carcinoma

Immunohistochemical Comparison of MUC1, CA125, and Her2Neu in Invasive Micropapillary Carcinoma of the Urinary Tract and Typical Invasive Urothelial Carcinoma With Retraction Artifact.

Sangoi AR, Higgins JP, et al:

Mod Pathol; 22 (May): 660-667

MUC1, CA125, and Her2Neu are not reliable for distinguishing the micropapillary variant of urothelial carcinoma from conventional cases with retraction artifact.

Background: Micropapillary carcinoma of the urinary bladder was first described in 1994, but more recently, it has been noted in the ureter and renal pelvis. As in other organs, such as the breast, lung, and colon, the micropapillary histologic variant tends to present with higher stage disease and conveys a poor prognosis. Some urological oncologists have suggested and recommended a different treatment strategy for micropapillary carcinomas, even if only superficially invasive. However, small biopsies and tissue artifacts can make distinction between micropapillary carcinoma variant and conventional carcinoma with retraction artifact difficult to interpret. Some investigators have reported on the immunophenotype of micropapillary carcinoma of the bladder, but a comprehensive evaluation with comparison to conventional urothelial carcinomas has not been performed.

Objective: To investigate the diagnostic utility of a panel of immunohistochemical stains to differentiate a micropapillary carcinoma from a conventional urothelial carcinoma with stromal retraction.

Methods: Biopsy or resection specimens from 24 cases of invasive micropapillary carcinoma of the urinary tract and 24 cases of typical urothelial carcinoma having prominent stromal retraction were collected and matched with clinicopathologic features as closely as possible. Two authors agreed on the H&E diagnosis of micropapillary variant, based on small nests or balls of cells within a lacunar space. Conventional carcinomas were described as having larger confluent nests within less prominent spaces that conformed to the shape of the tumor nest. Cases that were borderline or considered difficult to classify by morphology were excluded. Immunostains for MUC1, CA125, and Her2Neu were performed.

Results: Basal MUC1 staining was noted in 96% of the micropapillary variants and in 63% of the conventional cases. Membranous CA125 staining was noted in 33% of the micropapillary variants and in 13% of the conventional cases. Membranous Her2Neu staining 3+ was noted in 25% of micropapillary variants and in 8% of the conventional cases.

Conclusions: While invasive micropapillary carcinomas of the urinary tract more frequently stain for MUC1, CA125, and Her2Neu than do conventional carcinomas with stromal retraction, only the difference in MUC1 staining reached statistical significance.

Reviewer's Comments: These stains do not appear to be sensitive or specific for the micropapillary variant of urothelial carcinoma. Diagnosis should rest largely on the H&E interpretation.

Additional Keywords: Immunostaining

print tag: () Refer to original journal article.

Emerin Staining Reinforces PTC Nuclear Membrane Irregularities

Emerin Immunohistochemistry Reveals Diagnostic Features of Nuclear Membrane Arrangement in Thyroid Lesions.

Asioli S, Bussolati G:

Histopathol; 54 (April): 571-579

Emerin expression confirms the greater degree of nuclear membrane irregularity in papillary thyroid carcinoma compared with other thyroid lesions.

Background: Irregularities of the nuclear membrane (invaginations, knob-like protrusions, and intranuclear pseudoinclusions) are helpful in the diagnosis of many neoplasms, especially in papillary thyroid carcinomas (PTCs). The use of basic dyes, such as hematoxylin, highlights nuclear size, shape, and chromatin pattern. However, antibodies directed against other proteins specific to the nuclear membrane are more effective at revealing subtle irregularities of the nuclear membrane contour. Emerin is a nuclear lamin-binding protein localized to the inner aspect of the nuclear membrane.

Objective: To characterize the expression of emerin in normal thyroid tissues, in non-neoplastic thyroid tissues, and in follicular and papillary carcinomas.

Methods: 54 cases were studied, including 12 PTCs (6 classic and 6 follicular variants), and 6 cases each of follicular adenoma, follicular carcinoma, poorly differentiated carcinoma, Hashimoto's thyroiditis, microfollicular goiter, Grave's disease, and normal thyroid tissue. Following antigen retrieval, immunohistochemical staining of formalin-fixed, paraffin-embedded samples from each case was performed using a mouse monoclonal anti-emerin antibody (clone 4G5). Immunoperoxidase and immunofluorescence staining were performed, and images were acquired and analyzed using Image-Pro Plus image analysis software.

Results: Overall, use of the anti-emerin antibody resulted in well-defined localization of the nuclear membrane in epithelial cells of all cases. The details of the nuclear membrane were best seen using immunofluorescence staining, although immunoperoxidase preparations were also informative. Nuclei showed regular, round shapes and smooth membrane contours in cases of normal thyroid tissue and in most cases of goiter, Hashimoto's thyroiditis, follicular adenomas, and follicular carcinomas. In these cases (excluding normal thyroid tissue), occasional cells showed larger nuclei with subtle irregularities of the membrane contour, including so-called humps of membrane protruding from the nuclear membrane surface. In cases of PTC, there was consistent irregular infolding, curling, invagination, and formation of nuclear pseudoinclusions.

Conclusions: In contrast to normal thyroid tissue and other thyroid neoplasms, PTC undergoing emerin staining of the nuclear membrane demonstrates prominent foldings, deep invaginations, and intranuclear pseudoinclusions. These findings, although largely descriptive, may have diagnostic application in discriminating PTCs from other thyroid lesions.

Reviewer's Comments: As the authors mention, their findings are primarily descriptive and technical, although they certainly reinforce the classical teaching that nuclear membrane irregularities are more prominent in PTCs than in other thyroid lesions.

Additional Keywords: Emerin Staining

print tag: () Refer to original journal article.

Solitary Colorectal Polyps May Have Pure Schwann Cell Proliferations

Mucosal Schwann Cell "Hamartoma:" Clinicopathologic Study of 26 Neural Colorectal Polyps Distinct From Neurofibromas and Mucosal Neuromas.

Gibson JA, Hornick JL:

Am J Surg Pathol; 33 (May): 781-787

Colonic Schwann cell proliferation should be distinguished from neurofibromas and neuromas.

Background: Mesenchymal tumors occasionally present as polypoid lesions within the gastrointestinal tract. Neural and nerve sheath tumors include ganglioneuromas, granular cell tumors, perineuromas, schwannomas, neuromas, and neurofibromas. Distinction between these lesions is important as some neural lesions (neuromas and neurofibromas) are associated with inherited disease (MEN type 2B and type 1 neurofibromatosis, respectively).

Objective: To describe an uncommon entity of the gastrointestinal tract that can present as a polypoid lesion and show Schwann cell differentiation in the absence of ganglion cells.

Methods: The authors identified 26 similar polyps of the colon seen during a 20-year study interval. Most cases had been previously diagnosed as neuromas or neurofibromas. All lesions were composed of spindle cells, involved the mucosa, did not have ganglion cells, and were not better classified as a different well-described entity. H&E sections were reviewed, and features were compared to those of neurofibromas from patients with known neurofibromatosis type 1.

Results: All lesions were small and collected at colonoscopy. Most cases were from the rectosigmoid or descending colon. No patients had >1 of these polyps. At a mean follow-up of 5 years, no patients developed other neural polyps or were found to have neurofibromatosis type 1 or MEN type 2B. All polyps contained diffuse, unencapsulated spindle cell proliferations in the lamina propria that entrapped crypts. No whorling or palisading was present. The spindle cells were uniform and bland with elongated, tapering or wavy nuclei and abundant eosinophilic cytoplasm. The nuclei had fine chromatin and only occasional small nucleoli were identified. Mucosal ulceration, mitotic figures, and nuclear pleomorphism and atypia were not seen. All cases had strong and diffuse immunolabeling with antibodies to S100 protein. Antibodies to GFAP, EMA, claudin-1, CD34, SMA, and KIT were non-reactive. Neurofibromas appeared similar but were less uniformly cellular. They were also cytologically more heterogeneous. Neurofibromas only showed focal S100 protein immunoreactivity and displayed more axons with immunohistochemistry to neurofilament protein.

Conclusions: The authors suggest that their described lesions are distinct and should be distinguished from other neural lesions of the gut as they are not associated with inherited syndromes. They suggest the use of immunohistochemistry and the use of the term "mucosal Schwann cell hamartoma."

Reviewer's Comments: It is unclear how these lesions are to be distinguished from other Schwann cell lesions of the gut and whether deeper sections would ever display ganglion cells. Nonetheless, the authors correctly point out that the use of the term "neuroma" to refer to these lesions is problematic.

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Lab Testing Helps Predict Outcome, Guides Therapy in CLL

Guidelines for the Diagnosis and Treatment of Chronic Lymphocytic Leukemia: A Report From the International Workshop on Chronic Lymphocytic Leukemia Updating the National Cancer Institute-Working Group 1996 Guidelines.

Hallek M, Cheson BD, et al:
Blood; 111 (June 15): 5446-5456

Chromosomal abnormalities del(11q) and del(17p) are unfavorable predictors of outcome in cases of chronic lymphocytic leukemia and should be used for stratification in clinical trials.

Objective: To update diagnostic approaches, laboratory testing, and therapeutic strategies for the management of chronic lymphocytic leukemia (CLL).

Results: CLL is defined as a clonal proliferation of 5000 B lymphocytes/L (circulating small mature lymphocytes) accompanied by <55% prolymphocytes and should be distinguished from "monoclonal B-lymphocytoses," which are clonal proliferations numbering <5000/L without cytopenias or organomegaly. Bone marrow involvement by CLL can occur with peripheral blood tumor cells numbering <5000/L. The characteristic CLL phenotype is CD5+ CD19+ CD20(dim)+ CD23+ with dim surface immunoglobulin staining. Molecular cytogenetic abnormalities are demonstrable by FISH in 80% of cases and can be prognostically significant. Abnormalities del(11q) and del(17p) are unfavorable predictors of outcome, in contrast to normal karyotype or isolated del(13q), and should be used for stratification in clinical trials. Response to alemtuzumab may be predicted by del(17p). Other tests, which are not routinely recommended but may facilitate management of individual cases, include CD38 and ZAP-70 staining, both of which are unfavourable indicators when positive. Positive staining for ZAP-70 is highly correlated with absence of somatic mutation in the immunoglobulin heavy chain variable region (IgVH gene). These 3 tests are not part of routine general practice but are required for enrollment in clinical CLL trials. There is no evidence for survival advantage gained from treating early stage CLL with alkylating agents. Assessment for minimal residual disease by multicolor flow cytometry or PCR can be performed on blood, except within 3 months of therapy (especially monoclonal antibody therapy) when marrow sampling is required. Absence of MRD predicts favorable outcome.

Conclusions: In CLL, laboratory testing defines the disease, contributes significantly to prognostication, and will increasingly guide therapeutic decisions.

Reviewer's Comments: The authors acknowledge the need for improved standardization of ZAP70 testing but state that ZAP70 testing is required for clinical trial enrollment. Vigilant attention should be given to the methodology applied to ZAP70 testing in clinical trials. Random selection of one ZAP70 method in a clinical trial could lend endorsement to a non-reproducible laboratory approach, as we have seen for other diseases and other laboratory methods.

Additional Keywords: Diagnosis & Treatment

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Capillary II Fast Alternative for Monoclonal Immunoglobulins

Performance Comparison of Capillary and Agarose Gel Electrophoresis for the Identification and Characterization of Monoclonal Immunoglobulins.

McCudden CR, Mathews SP, et al:
Am J Clin Pathol; 129 (March): 451-458

Automated capillary electrophoresis methods are comparable to traditional agarose gel and immunofixation screening for serum monoclonal immunoglobulins but require confirmatory immunofixation in some cases.

Background: Traditional agarose gel electrophoresis (AGE) and immunofixation electrophoresis (IFE) remain as standard methods for identification of serum monoclonal gammopathies. Rapid, automated capillary electrophoresis (CE) methods are reported to be comparable, with greater sensitivity but lower specificity than AGE. Subtraction immunotyping (IT) involves comparison of capillary serum protein electrophoresis performed on serum with or without pre-incubation with antisera for gamma , alpha , and heavy chains and kappa and lambda light chains.

Objective: To compare interobserver variability in interpretation of traditional AGE and IFE methods versus automated CE and subtraction IT electrophoresis methods as screening tests for serum monoclonal immunoglobulins.

Methods: 149 consecutive serum protein electrophoresis specimens were analyzed by AGE and IFE on the Hydrasys (Sebia, Norcross, GA) using amido black staining and scanning densitometry and compared with analysis using CE and IT methods on the Capillarys II (Sebia). Results were evaluated by 5 interpreters. For 146 out of 149 specimens (98%), there was 100% concordance of IFE results among the 5 interpreters. These 146 specimens were included in the study.

Result: The methodologic limit of monoclonal immunoglobulin quantification was =0.3 g/dL (3 g/L). Among 146 specimens, 91 (62%) demonstrated a monoclonal immunoglobulin by IFE. CE was slightly more sensitive (91.5%) than AGE (90.9%) but was less specific (73.7%) than AGE (91.0%) in detecting monoclonal proteins. IT had the lowest sensitivity (84.9%) but the highest specificity (93.8%). Among the 91 positive specimens identified by IFE, 86 were interpreted as abnormal using CE or IT. IFE had the highest interobserver agreement (78%) and IT had the lowest (62%). In 5 of 9 hypogammaglobulinemic specimens with a monoclonal paraprotein, IT was misinterpreted by some reviewers.

Conclusion: Automated capillary electrophoresis methods are comparable to traditional AGE and IFE as screening tests for serum monoclonal immunoglobulins but require confirmatory immunofixation in some cases, especially hypogammaglobulinemic specimens.

Reviewer's Comments: The authors' test strategy includes reflexing mildly abnormal automated capillary electrophoresis results to immunofixation alone, which avoids duplicate immunofixation-subtraction immunotyping.

Additional Keywords: Monoclonal Gammopathy

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CSF Cytology Not Predictive of NM Survival

Neoplastic Meningitis: Survival as a Function of Cerebrospinal Fluid Cytology.

Chamberlain MC, Johnston SK:

Cancer; 115 (May 1): 1941-1946

The presence or absence of cerebrospinal fluid cytology did not show a significant difference in survival in patients with neoplastic meningitis.

Background: Neoplastic meningitis (NM) is a frequent complication of systemic cancer. The presence of NM is associated with end-stage cancer and/or bulky central nervous system (CNS) disease. Therefore, deciding who will benefit from treatment is a challenge. The National Comprehensive Cancer Network stratifies patients with NM into poor-risk and good-risk groups. Poor risk factors for treatment of NM include a low functional score, multiple serious neurologic deficits, and extensive systemic disease with few treatment options. Only approximately 50% to 60% of patients with clinically diagnosed NM have malignant cells in cerebrospinal fluid (CSF) cytology specimens.

Objective: To evaluate whether the presence or absence of CSF involvement as demonstrated by cytology is a predictive factor for survival in patients with NM.

Methods: Two groups of patients were retrospectively selected during a 17-year study interval. Forty-two patients diagnosed with NM and a positive CSF cytology were selected for group A. Each patient in group A was matched with a patient with a clinical diagnosis of NM and negative CSF cytology (group B) with respect to age, gender, tumor type, extent of disease, site of NM disease, treatment, and performance status. A clinical diagnosis of NM was defined as a clinical syndrome consistent with NM in a patient with known cancer, abnormal CSF profile, and neuroradiography consistent with NM. All patients (groups A and B) were treated with at least intraventricular chemotherapy and involved-field radiotherapy.

Results: The characteristics of groups A and B were statistically similar. No treatment-related deaths occurred. Survival did not significantly vary between groups. The overall median survival rates for groups A and B were 18 weeks and 20 weeks, respectively. There was a trend toward improved 3-month and 6-month survival in patients with a negative CSF cytology compared to those with a positive CSF cytology (90% vs 83% at 3 months and 40% vs 33% at 6 months, respectively), but there was no difference in 12-month survival (9% in both groups).

Conclusion: In patients with NM who were matched for known prognostic variables, the presence or absence of CSF cytology did not show a significant difference in survival.

Reviewer's Comments: This study looks at a subset of patients with known NM (either pathologic or clinical diagnosis) and treated. In our institution, most CSF samples from patients with known cancer are part of a workup to make the diagnosis of NM, particularly in cases which do not meet the clinical definition. It is important to remember that CSF cytology sensitivity is low for the diagnosis of NM.

Additional Keywords: Predicting Outcome

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LECs Not Linked to EBV or IgG4 Autoimmune Disease

Lymphoepithelial Cyst of the Parotid Gland: Its Possible Histopathogenesis Based on Clinicopathologic Analysis of 64 Cases.

Wu L, Cheng J, et al:

Hum Pathol; 40 (May): 683-692

Lymphoepithelial cysts of the parotid do not appear to be associated with IgG4-positive autoimmune disease or Epstein-Barr virus infection.

Background: Lymphoepithelial (LE) cysts arise in the head and neck. One of the major sites for LE cysts is the parotid gland. The mechanism of development for these lesions remains controversial. There is a strong association with HIV infection, but LE cysts occur in non-HIV infected individuals as well.

Objective: To present the largest series of non-HIV-related LE cysts and their clinicopathologic features.

Methods: Patients from 1 institution with a diagnosis of LE cyst in the parotid gland were obtained during a 29-year study interval. Clinical data were obtained, including age, size, symptoms, and HIV status. Histologic features were recorded, including capsule development, cyst epithelial lining, and lymphoid association. Immunohistochemistry was performed with antibodies to pankeratin, CD20, CD45RO, Ki-67, podoplanin, and IgG4. PCR and in-situ hybridization for EBV DNA and RNA was performed on each case, respectively.

Results: 64 patients (28 male, 36 female) with a mean age of 52 years were included. In most cases, the chief symptom was painless swelling. No patients had symptoms of or a diagnosis of Sjogren's disease. Histologically, LE cysts were classified into 3 types. Type I cases (n=9) most resembled a dilated duct in focal sialadenitis; the cyst was small and lined by columnar epithelium, and the lymphocytic infiltrate infiltrated adjacent parotid tissue and did not show follicle formation. Type II cases (n=27) had partially encapsulated cysts lined by flat or nonkeratinizing squamous epithelium; the surrounding lymphocytic infiltrate was partially encapsulated and had occasional follicles. Type III cases (n=28) had larger well-encapsulated cysts lined by nonkeratinizing squamous epithelium with abundant lymphoid follicles in the surrounding lymphoid tissue. A mixture of B and T lymphocytes were present in all forms, although germinal center formation was largely restricted to type III lesions, and rarely in type II lesions. No cases demonstrated increased IgG4 cells as would be expected in an autoimmune sclerosing disease. Lymphatic spaces (as demonstrated by podoplanin) were best developed in type III lesions. No cases demonstrated EBV by PCR or in situ hybridization.

Conclusion: These results suggest that there is a progression of development in parotid LE cysts, from type I to type III lesions. If true, this supports a sialadenitis-based origin, with lymphoid stroma developing alongside cyst formation. However, there is no evidence to support a link with Sjogren's disease or other IgG4-related autoimmune disease.

Reviewer's Comments: This well-designed study is the largest and, to date, only comprehensive evaluation of the histology of LE cysts of the parotid not associated with HIV disease.

Additional Keywords: Lymphoepithelial Cyst

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Gene Signatures Useful for Differentiating Melanoma, Nevi

Molecular Classification of Melanomas and Nevi Using Gene Expression Microarray Signatures and Formalin-Fixed and Paraffin-Embedded Tissue.

Koh SS, Opel ML, et al:

Mod Pathol; 22 (April): 538-546

Gene expression profiles from formalin-fixed and paraffin-embedded melanocytic tissue accurately classify melanomas and nevi into their histopathologic diagnosis.

Background: The histological diagnosis of melanoma can be difficult, especially in cases that have features overlapping with a benign nevus. However, the under-diagnosis of malignant melanoma can lead to a failure for proper management, representing the second largest group of malpractice claims. Given the findings from cell lines and frozen tissues implying that molecular changes may reflect metastatic potential and clinical outcomes, extension of these results to formalin-fixed and paraffin-embedded tissues could provide a clinically useful test.

Objective: To compare melanomas and nevi using gene expression arrays from formalin-fixed and paraffin-embedded tissues.

Methods: Melanocytes were isolated by laser capture microdissection from 165 benign nevi and malignant melanomas tissue blocks diagnosed by routine morphologic criteria by 2 to 4 pathologists. All were from procedures performed within 3 years, and the blocks had an average storage time of 1 year. RNA was extracted and amplified, and then DNA microarray hybridizations were conducted. A subset was used for clustering analysis and another was used for testing the classifiers in a blinded study. RT-PCR was then used to verify the results.

Results: Unsupervised hierarchical clustering of melanocytic lesions detected 2 distinct molecular phenotypes which were closely correlated to the histologic groups of melanomas (95% concordance) and nevi (98% concordance). This was based on 36 differently expressed genes, including those involved in signal transduction, transcription, and cell growth. These identified genes were then used to subclassify a group of unknown melanocytic lesions into melanomas and nevi, having a good concordance rate with the histopathologic diagnosis (89% concordance overall).

Conclusions: Molecular techniques may be applied to formalin-fixed and paraffin-embedded melanocytic lesions to assess for gene signatures that correspond to the histopathologic diagnoses of melanoma and benign nevus.

Reviewer's Comments: The authors found distinct molecular signatures from gene expression profiling that correlated to the histopathologic classification of benign and malignant melanocytic lesions. The diagnostic application of this process should also be explored in melanocytic lesions that are more difficult to interpret histologically, where adjunct methods are more likely to be utilized.

Additional Keywords: Molecular Classification

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P21 Predicts Outcome in HPV-Related Tonsillar Carcinomas

P21Cip1/WAF1 Expression Is Strongly Associated With HPV-Positive Tonsillar Carcinoma and a Favorable Prognosis.

Hafkamp HC, Mooren JJ, et al:

Mod Pathol; 22 (May): 686-698

Human papillomavirus (HPV)-positive tonsillar squamous cell carcinomas tend to overexpress p21 and p14, but the expression of p21 is a favorable prognostic feature, even in the absence of HPV.

Background: The human papillomavirus (HPV) has been demonstrated to be involved in the carcinogenesis of squamous cell carcinomas of the head and neck, particularly in those of the tonsillar tissues. The prognosis of HPV-related head and neck cancers has been shown to be considerably better than those associated with tobacco or alcohol use, despite being described as poorly differentiated and having a high frequency of nodal metastases at presentation. The HPV-derived oncoproteins E6 and E7 can alter expression of cell cycle proteins in the pRb pathway, while those not associated with HPV tend to have p53 alterations.

Objective: To characterize the expression of cell cycle proteins from the pRb pathway and p53 cascade in tonsillar squamous cell carcinomas with known HPV16 status and outcome data.

Methods: Tonsillar squamous cell carcinomas with known HPV16 status (by in situ hybridization analysis) were collected and immunostained for Ki67, p16, cyclin D1, pRb, p14, MDM2, p53, p21, and p27.

Results: 77 cases were examined. Of these, 35% had integrated HPV16 DNA and p16 expression. The age and gender distributions were similar between the 2 groups, but smoking and alcohol consumption was seen significantly more often in patients with non-HPV tumors. These HPV-related tumors overexpressed p14 and p21 with downregulation of pRb and cyclin D1 compared to the non-HPV-related tumors. Multivariate analysis demonstrated that only positive smoking status, tumor size 4 cm, strong cyclin D1, and no/low p21 expression were independent negative prognostic factors.

Conclusions: HPV16-positive tonsillar squamous cell carcinomas tend to overexpress cell cycle proteins p21 and p14 from the pRb pathway with downregulation of pRb and cyclin D1. Tumor size (<4 cm) and strong p21 were the best independent predictors for a favorable outcome.

Reviewer's Comments: Expression of p21 was one of the strongest predictors of outcome, even independent of HPV status. Surprisingly, lymph node status had little value as a prognostic factor.

Additional Keywords: HPV-Related

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Pediatric Collagenous Gastritis Presents With Anemia

Collagenous Gastritis: Histopathologic Features and Association With Other Gastrointestinal Diseases.

Leung ST, Chandan VS, et al:

Am J Surg Pathol; 33 (May): 788-798

Collagenous gastritis in adults frequently presents with other autoimmune disease.

Background: Aside from collagenous colitis, the collagenous enteritides are very uncommon. Collagenous colitis is characterized by the deposition of subepithelial collagen usually with abundant intraepithelial lymphocytes. Endoscopy usually cannot identify any changes grossly. The literature regarding collagenous gastritis is sparse, and some cases have been reported with other gastrointestinal or autoimmune disorders. Cases have been reported that have endoscopically shown erythema and nodularity.

Objective: To review the histologic and clinical findings of a small series of patients with collagenous gastritis.

Methods: The surgical pathology files from a single institution were reviewed for all cases of collagenous gastritis. For the diagnosis of collagenous gastritis, subepithelial collagen deposition was necessary. All gastrointestinal biopsies were reviewed. Gastritis was classified as per the updated Sydney system. Trichrome stains were performed, and specimens were assessed for lymphocytic gastritis. Clinical and follow-up information were pursued.

Results: Of the cases collected, 12 were considered compatible with the diagnosis of collagenous gastritis. There was an equal number of men and women, and the mean age was 44 years. Four patients were younger than 20 years old. Most of the young patients presented with anemia and nodularity, whereas the adult patients frequently presented with other autoimmune diseases. Of the 8 adult patients, 3 had celiac sprue, 1 had collagenous sprue, and 1 had collagenous colitis. Three of the adult patients had atrophic-appearing stomach endoscopically, and 4 had nodular-appearing mucosa. Follow-up was available for 8 patients. Two of 3 pediatric patients showed improvement with medical therapy, and 3 adults with sprue showed improvement with gluten-free diets. The patient with collagenous sprue did not improve with steroid therapy. Collagen deposition was increased in both the antrum and fundus and was both patchy and diffuse. Epithelial flattening was frequently seen. All cases showed chronic inflammation, and 5 showed acute inflammation. Three patients had lymphocytic gastritis. *Helicobacter pylori* was not identified in any of the 12 cases. Intestinal metaplasia eventually developed in 1 case.

Conclusions: Collagenous gastritis is frequently associated with other collagenous GI diseases, celiac sprue, chronic inflammation, lymphocytic gastritis, and autoimmune disease, in general. Pediatric patients frequently present with anemia.

Reviewer's Comments: This paper presents a large series of patients with collagenous gastritis. The association with a myriad of diseases and variable follow-up suggests that this may be a nonspecific finding rather than a particular disease.

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PAX5 May Help Differentiate ARMS From ERMS

PAX Immunoreactivity Identifies Alveolar Rhabdomyosarcoma.

Sullivan LM, Atkins KA, LeGallo RD:

Am J Surg Pathol; 33 (May): 775-780

Alveolar rhabdomyosarcomas frequently show immunoreactivity with antibodies to PAX5.

Background: Rhabdomyosarcomas are the most common soft tissue malignancies in children. They are generally subtyped as either embryonal rhabdomyosarcomas (ERMS) or alveolar rhabdomyosarcomas (ARMS) based on histologic features, although occasionally this can be difficult, such as with small biopsies. However, the distinction is important because it carries both prognostic and therapeutic implications. Cytogenetic analysis can be particularly helpful with such cases when it identifies ARMS-specific translocations, either the t(1;13) or t(2;13), which juxtapose the FKHR gene with the PAX7 and PAX3 genes, respectively. No immunohistochemical stains have been shown to consistently distinguish the rhabdomyosarcoma subtypes.

Objective: To investigate the possible use of antibodies to PAX5, a marker of B-cell differentiation, to assist in differentiation ERMS and ARMS.

Methods: A tissue microarray was constructed with various pediatric small blue cell tumors seen at a single institution. Additionally, two tissue microarrays of unique rhabdomyosarcomas were used. Immunostaining was performed with antibodies to PAX5, and nuclear staining was scored semiquantitatively. Results were compared with cytogenetic results when available.

Results: 55 cases of ERMS and 51 cases of ARMS were evaluated. No ERMS cases showed nuclear immunoreactivity, whereas two-thirds of the ARMS cases showed nuclear staining to varying degrees. Also of note, 100% of Wilms tumors and B-cell lymphoblastic lymphomas showed staining, whereas no staining was seen in neuroblastomas, Ewing Family of Tumors, T-cell lymphoblastic lymphomas, hepatoblastomas, and granulocytic sarcomas. Of those tumors with cytogenetic data, 5 ARMS cases with characteristic translocations showed immunostaining with antibodies to PAX5, whereas the 2 with atypical cytogenetic findings did not show staining.

Conclusions: The proper subtyping of rhabdomyosarcomas is essential because children with ARMS tend to do worse and receive more intense chemotherapy than do those with ERMS. For occasional cases that are difficult to subtype based on conventional sections and for which cytogenetic testing is not possible, immunostaining with antibodies to PAX5 may be helpful.

Reviewer's Comments: This paper is one of the first to demonstrate a possible immunostain for distinguishing ARMS and ERMS. It will be interesting to see if larger studies confirm the correlation with cytogenetic findings.

Additional Keywords: Immunohistochemistry

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Include Amebic Colitis in Differential Diagnosis of Suspected IBD

Amebic Colitis Can Mimic Tuberculosis and Inflammatory Bowel Disease on Endoscopy and Biopsy.

Pai SA:

Int J Surg Pathol; 17 (April): 116-121

Remember to look for the trophozoites of *Entamoeba histolytica* in suspected cases of infectious colitis and inflammatory bowel disease.

Background: Infection with *Entamoeba histolytica* is most commonly seen in developing countries and usually causes a mild to severe gastrointestinal illness characterized by abdominal pain and diarrhea with or without bleeding. Since these clinical findings may be seen in other infectious diseases and inflammatory bowel disease (IBD), patients sometimes undergo endoscopic examination with colon biopsy to identify the true cause. Incorrectly treating amebiasis with steroids rather than metronidazole may have devastating consequences.

Objective: To describe the clinical and histopathological findings in patients with amebic colitis.

Methods: The authors identified 11 cases of amebic colitis recorded at the Manipal Hospital in Bangalore, India, between 2001 and 2007. For each case, relevant clinical information was recorded, and H&E and PAS-stained slides from endoscopic biopsies were retrieved and reviewed.

Results: Patient ages ranged from 21 to 50 years. Presenting symptoms included various combinations of dyspepsia, abdominal pain, diarrhea with or without blood, fever, vomiting, weight loss, incomplete evacuation, and blood per rectum. Endoscopic findings included small ulcers, deep ulcers, and white slough with variable involvement of the ascending, transverse, and descending colon, cecum, ileocecal valve, and rectum. The endoscopic differential diagnosis variably included Crohn's disease, ulcerative colitis, tuberculosis, solitary rectal ulcer syndrome, enteric fever, and amebiasis. Only 1 of the patients had a routine stool exam, in which *Giardia lamblia* was identified. Biopsy findings included mucosal ulceration (n=11), mucin depletion (n=11), cryptitis (n=6), and crypt abscess formation (n=1). No crypt branching was identified in any case. *E histolytica* trophozoites were present within superficial exudate in all cases. The trophozoites had prominent nucleoli and phagocytosed erythrocytes, and they measured between 25 to 40 micrometers in diameter.

Conclusions: There is overlap between the various clinical and histopathological features of amebic colitis and other causes of infectious colitis, as well as IBD. These include evidence of chronic mucosal injury, cryptitis, and crypt abscess formation. Thus, one must diligently search for *E histolytica* before rendering a diagnosis of IBD or other cause of infectious colitis.

Reviewer's Comments: Although less common in Western countries, increased foreign travel has made recognition of *E histolytica* infection important for all physicians. The authors stress the importance of identifying phagocytosed erythrocytes within the *E histolytica* trophozoites, since these are not seen in the nonpathogenic amebae *E dispar*.

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Look for Signs of Malignancy in Cases of Struma Ovarii

Histologically Bland "Extremely Well Differentiated" Thyroid Carcinomas Arising in Struma Ovarii Can Recur and Metastasize.

Garg K, Soslow RA, et al:

Int J Gynecol Pathol; 28 (May): 222-230

Even very well-differentiated tumors arising in struma ovarii have the potential to recur and/or metastasize.

Background: Struma ovarii (SO) is a monodermal teratoma in which >50% of the tumor is composed of thyroid tissue. Recent studies have supported the view that a malignant diagnosis should be based on the same features used in diagnosing primary carcinomas of the thyroid.

Objective: To review all cases of so-called malignant SO (MSO) from a large referral institution, and to characterize the clinical and pathologic features of these cases.

Methods: During a 15-year study interval at a major cancer referral hospital with an average annual specimen volume of 45,000 cases, only 10 cases of MSO were identified. All H&E-stained slides from each case were separately reviewed by 3 pathologists with expertise in thyroid and ovarian neoplasia. MSO was diagnosed using the same criteria employed for malignant tumors in the eutopic thyroid gland. Tumors with characteristic nuclear features and at least focal papillary architecture were diagnosed as classic papillary thyroid carcinoma (PTC). Tumors with the same nuclear findings but with at least 99% follicular growth were diagnosed as the follicular variant of PTC (FVPTC). Tumors with solid growth, necrosis, and/or 5 or more mitotic figures per 10 HPFs were diagnosed as poorly differentiated carcinoma (PDC).

Results: All 10 patients presented with disease initially confined to the ovary: 8 patients had pelvic-related symptoms and 2 patients had tumors discovered incidentally during pregnancy. Tumor types included 2 classic PTC, 6 FVPTC, and 2 PDC. Two of these cases originally diagnosed as "benign" struma presented with pelvic dissemination of PTC at 3 and 4 years after the initial diagnosis, both of which were seen in young pregnant women originally diagnosed with ovarian cysts. Retrospective review of the ovarian cyst from 1 of the patients showed features of FVPTC, while review of the tissue from the second patient showed findings suggestive but not diagnostic of PTC. Six years after the initial diagnosis of MSO, followed by thyroidectomy and treatment with radioactive iodine, both patients are alive.

Conclusions: The likelihood for aggressive clinical behavior seems unrelated to tumor grade or tumor type. Since both patients who developed metastatic disease shared similar clinical characteristics, the authors raise the possibility that the hormonal milieu during pregnancy may influence the development of MSO. Care of such patients requires close follow-up.

Reviewer's Comments: The small size of the series is to be expected given the rarity of MSO. Adequate sampling and careful slide review should be performed in all cases of SO.

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