Clear cell renal cell carcinomas with a deletion of 9p are associated with an aggressive disease course, even when presenting as small, localized renal tumors.

**Background:** Increasing numbers of small, incidentally discovered renal cell tumors are identified with use of high-resolution abdominal imaging. Knowledge of which small tumors are more likely to metastasize would allow early patient selection for adjuvant therapy. Clear cell renal cell carcinoma (ccRCC) is typically associated with abnormalities of chromosome 3p, which are associated with less aggressive disease; however, a small subset of ccRCC has deletions of chromosome 9p. In this study, the authors evaluate the prognostic significance of 9p deletions in the largest cohort to date of ccRCC patients.

**Objective:** To determine the prognostic significance of chromosome 9p deletion in ccRCC.

**Methods:** A tissue microarray was constructed using 3 tumor cores from 316 surgically resected ccRCCs. Fluorescence *in situ* hybridization (FISH) was performed using dual color probes for the centromere of chromosome 9 (green signal) and a portion of 9p (red signal). Number of red and green signals per nucleus was counted in each core by 2 independent investigators. Tumors with 2 red and 2 green signals were considered normal, tumors with 1 red and 2 green signals were considered 9p deleted, and tumors with 1 red and 1 green signal were considered chromosome 9 monosomic. At least 2 of 3 tumor cores were required to display an abnormal pattern to be designated as 9p deleted. An additional 388 ccRCCs were procured fresh at time of surgery for conventional cytogenetic analysis using G-banding. Clinicopathologic features and follow-up events were recorded.

**Results:** Of 703 ccRCCs, 97 (14%) had 9p deletions, of which most were monosomy 9. The 9p-deleted tumors were significantly associated with higher tumor stage, increased tumor grade, and presence of metastasis. Median disease-specific survival for patients with and those without 9p deletion was 37 months and 82 months, respectively. On multivariate analysis, presence of a deletion of 9p continued to be an independent marker of worse disease-specific survival. In the subset of patients who presented with localized, small (<4 cm) renal tumors, those with tumors harboring a 9p deletion recurred 19% of the time compared with 2% of patients without a deletion. Five-year recurrence-free survival in this subset of patients with and in those without 9p-deleted tumors was 68% versus 97%, respectively.

**Conclusions:** Approximately 14% of ccRCCs have deletions of chromosome 9p, and these tumors are associated with an aggressive disease course, even when presenting with small, localized renal tumors.

**Reviewer's Comments:** This well-designed study demonstrates a significant prognostic impact in ccRCCs on the basis of cytogenetics. The FISH probe for 9p is readily commercially available as part of the UroVysion (Vysis, Downers Grove, Ill) bladder tumor assay and could be readily adapted to this use. (Reviewer-Deborah J. Chute, MD).

© 2010, Oakstone Medical Publishing

Keywords: Kidney Cancer, Renal Cell Carcinoma, Chromosome 9p, Prognosis, Biomarkers

Print Tag: Refer to original journal article
Features in core biopsies that predict phyllodes tumor on excision include marked stromal cellularity, marked nuclear atypia, stromal overgrowth, ≥2 mitotic figures per 10 high-power fields, and ill-defined lesional borders.

**Background:** Fibroepithelial lesions of the breast are composed of both epithelial and stromal elements. On core needle biopsies, sometimes it is difficult to distinguish between the main fibroepithelial lesions (fibroadenoma and phyllodes tumor) because of sampling issues or because both lesions share certain histological features. For this reason, many pathologists advocate using descriptive terminology (such as "cellular fibroepithelial lesion") when reporting these lesions if any diagnostic uncertainty exists. In such settings, excision of the lesion for more complete evaluation is the next step in management. There are only a few studies cited by the authors of this study that attempt to distinguish between fibroadenoma and phyllodes tumor on core biopsy using histological features and immunohistochemical markers.

**Objective:** To determine key histological and biological features that will increase the positive predictive value of preoperative breast core biopsies of fibroepithelial lesions.

**Methods:** 261 fibroepithelial lesions diagnosed on core biopsy were included. Biopsies were from patients ranging from ages 20 to 79 years with nodular lesions detected radiographically. Of 261 cases, diagnoses included fibroadenoma or favor fibroadenoma (n=157), phyllodes tumors that were definitively diagnosed, favored, or could not be excluded (n=82), fibroepithelial lesion not otherwise specified (n=20), and pseudoangiomatous hyperplasia (n=2). In 98 cases (37%), phyllodes tumor could not be excluded. Of these, 57 (58%) had subsequent open excision biopsies. These latter cases were evaluated for stromal hypercellularity, nuclear atypia, stromal mitotic figures, stromal overgrowth, epithelial fronding, epithelial hyperplasia, an ill-defined lesional edge, presence of pseudoangiomatous hyperplasia, and adipose tissue. In addition, immunohistochemical staining for Ki-67, topoisomerase IIa, CD34, CD117, and Bcl-2 was performed. Findings were then compared with results of subsequent excision biopsies.

**Results:** Features in core biopsies that predicted phyllodes tumor on excision included marked stromal cellularity, marked nuclear atypia, stromal overgrowth, ≥2 mitotic figures per 10 high-power fields, and ill-defined lesional borders. Staining with Ki-67 (>5%), topoisomerase IIa (>5%), and reduced/patchy CD34 expression showed a significant correlation with a subsequent phyllodes diagnosis.

**Conclusions:** Phyllodes tumors can be predicted on core needle biopsies based on presence of stromal hypercellularity combined with other key histological features, results of Ki-67, topoisomerase IIa and CD34 immunohistochemical staining, and clinical findings.

**Reviewer's Comments:** Despite these helpful features, some cases will surely remain problematic. One other consideration not addressed in this article is the issue of subclassifying phyllodes tumors into benign, borderline, and malignant categories. Although the criteria for diagnosis are still controversial, the most recent WHO scheme provides helpful guidance. For malignant phyllodes tumors, in particular, one should see marked stromal hypercellularity and cytologic pleomorphism, high mitotic activity, invasive borders, and marked stromal overgrowth. (Reviewer-T. David Bourne, MD).

© 2010, Oakstone Medical Publishing

Keywords: Fibroepithelial Breast Lesions, Core Biopsy

Print Tag: Refer to original journal article
Randomized mandatory second review of surgical pathology reports prior to sign-out may lead to improved patient safety.

**Background:** As medical centers continue to have to document efforts to improve patient safety, there are increased efforts in anatomic pathology for quality improvement (QI) and quality assurance (QA). Incorporation of these practices into daily activities often proves difficult, however. Most QA or QI practices in anatomic pathology are audits in nature, such as the required review of all cases of newly diagnosed malignancy.

**Objective:** To investigate the function of a prospective auditing tool at an academic center that uses subspecialty sign-out.

**Methods:** 1 department's lab information system was modified to implement a 5% and then an 8% review system for surgical pathology cases. This system notifies the primary pathologist at time of sign-out that a case has been selected for mandatory review when the electronic signature has been entered. The pathologist is blinded to this activity prior to finalization of the report. A reviewing pathologist is then required to review and sign the case out within a 24-hour period. The reviewing pathologist can then indicate agreement, minor disagreement, moderate disagreement, or major disagreement. A third pathologist must then review any disagreement. The authors monitored 14 months of use with particular attention to turnaround time, number and level of disagreements, and number of report amendments.

**Results:** A prospective review system allowed for an increased review rate as cases were easier to locate when immediate review was required. Case turnaround time was unchanged for those requiring a second review when compared to those not undergoing a second review. Number of total amendments fell 30% during the period that a prospective review was used. Editing of actual diagnoses decreased 55% with the prospective review system in place.

**Conclusions:** Prospective review allows for easier review of a selected group of cases when compared to retrospective review and, thus, allows for easier attainment of goal review percentages. It does not affect case turnaround time, and it decreases the need for case amendment.

**Reviewer's Comments:** A random prospective review sounds like an effective means of QA implementation for a busy surgical pathology laboratory. Decreased amendments likely correlate with a decreased risk for patient harm. (Reviewer-Erward B. Stelow, MD).

© 2010, Oakstone Medical Publishing

Keywords: Quality Assurance, Second Review, Amendment, Turnaround Time

Print Tag: Refer to original journal article
Is ERG Rearrangement Specific to Prostate Cancer?

ERG Rearrangement Is Specific to Prostate Cancer and Does Not Occur in Any Other Common Tumor.

Scheble VJ, Braun M, et al:
Mod Pathol 2010; 23 (August): 1061-1067

ERG is a relatively prostate cancer-specific genetic alteration that may prove to have clinical application.

**Background:** Most cancers derive from acquisition of various somatic genetic alterations. Until recently, recurrent translocations were thought to only be specific for hematological and soft tissue malignancies. Subtypes of breast, thyroid, and renal carcinomas were first noted to harbor translocations, which has led to the discovery of recurrent gene rearrangements in the majority of prostate cancers. These rearrangements involve various androgen-regulated 5’ partners and ETS genes, most commonly resulting in a gene fusion involving ERG. Some of the ETS genes have previously been detected in translocations in Ewing's sarcoma, acute myelogenous leukemia, and breast cancer but typically not the ERG gene.

**Objective:** To survey a variety of common tumors for evidence of ERG rearrangements known to be common in prostate cancer, and to identify the somatic copy number alterations specific for prostate cancer from a published data set of cancer specimens.

**Methods:** 2942 tumor samples representing 54 different common malignant and benign neoplasms were evaluated for ERG rearrangement using a break-apart fluorescence in situ hybridization (FISH) assay performed on constructed tissue microarrays. The FISH assay distinguished between insertion and interstitial deletion. ERG rearrangement frequency was also established for prostate cancer using 109 consecutive partially PSA screen-detected adenocarcinomas from prostatectomy specimens. Estimates of somatic copy number alterations were obtained from published single nucleotide polymorphism (SNP) data.

**Results:** None of 2261 non-prostate neoplasms that were assessable by FISH were determined to harbor rearrangement of the ERG locus. In contrast, 54 of 109 prostate cancers (49.5%) were determined to have rearrangement of ERG. Of these, 40 (74.1%) were deletions, and 14 (25.9%) were insertions. Of 26 tumor types assessed for copy number by SNP data, the TMPRSS2 and ERG (21q22.2-3) deletion site was detected only in prostate cancer.

**Conclusions:** Although other malignancies may only rarely have rearrangements involving ERG, they are common and specific to prostate cancer, especially the distinct deletion site between TMPRSS2 and ERG.

**Reviewer’s Comments:** Finding a common but specific genetic alteration in prostate cancer is significant because it has the potential for application in detection, diagnosis, and treatment. (Reviewer-Mary T. Galgano, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cancer, ERG Alterations

Print Tag: Refer to original journal article
Consider *Penicillium marneffei* in bone marrow from an immunosuppressed Asian patient with a marrow biopsy demonstrating a prominent histiocytic response.

**Background:** *Penicillium marneffei* is a thermally dimorphic fungus that is a common cause of opportunistic infections, especially in immunocompromised patients in Southeast Asian countries. Characteristic features include a "broom-like" arrangement of branching phialides giving rise to a chain of conidia. The fungus produces a diffusible red pigment. The bone marrow is a frequent site of involvement in disseminated penicilliosis and sometimes provides the first clue to the diagnosis.

**Objective:** To review pathologic findings in the bone marrow in AIDS patients from Hong Kong with involvement by penicilliosis.

**Methods:** The cases span a 20-year period, and 72 patients with culture-proven *P. marneffei* infection were identified. Of these patients, 17 underwent marrow aspiration and trephine biopsy. Sixteen patients were male.

**Results:** 16 cases had identifiable marrow involvement; in 11 cases, this preceded the microbiologic culture confirmation. Average turnaround time for culture was 12 days compared to 7 days for marrow results. The author notes the yield would have been higher if silver staining had been performed on all cases irrespective of initial marrow findings. Peripheral blood findings demonstrated bi- or pancytopenia with mild-to-moderate thrombocytopenia in most cases. In 4 cases, circulating monocytes with ingested yeast forms were identified. On marrow aspiration, the most prominent finding was a histiocytic proliferation, which sometimes demonstrated engorged histiocytes with numerous (>100) yeast forms. The yeast forms appeared as small, basophilic inclusions with an eccentric or central dot-like inclusion. Some showed a transverse septum, and none showed budding. *P. marneffei* infection was identified in 9 of 17 cases that were biopsied. Just as in the aspirates, a reactive histiocytic proliferation with identifiable yeast forms of varying amount was the most prominent finding. The yeast forms measured 2 to 5 µm in size (approximately one fourth the size of a red blood cell) and were highlighted by a silver methenamine stain.

**Conclusions:** Most patients with *P. marneffei* infection usually have disseminated disease. Complicating this is that, especially in AIDS patients, anergy may result in the lack of a prominent histiocytic response making identification challenging. Thus, careful examination aided with special stains is important in these cases.

**Reviewer's Comments:** At the University of Virginia, we not uncommonly see *Histoplasma capsulatum* in specimens such as bronchioloalveolar lavages; however, although the yeast forms are similar, narrow-based budding is characteristic of *Histoplasma*. Furthermore, the geographic location is helpful. While this may be rare outside of the endemic region, with more foreign travel and more immunosuppressed patients being seen (ie, bone marrow transplant patients), one should at the very least order special stains when faced with granulomas or a suspicious history. (Reviewer-William A. Kanner, MD).

© 2010, Oakstone Medical Publishing

**Keywords:** *Penicillium marneffei*, Bone Marrow

**Print Tag:** Refer to original journal article
Encapsulated follicular variant of papillary thyroid carcinoma (PTC) has a high rate of RAS mutation similar to that of follicular adenoma/carcinoma, but infiltrative follicular variant has a high rate of BRAF mutations similar to that of classic PTC.

**Background:** Papillary thyroid carcinoma (PTC) is histologically defined by optically clear nuclei that are enlarged and overlapping with grooves and inclusions. Architecturally, PTC is composed of a mixture of papillae and follicles, but the follicular variant describes those composed entirely of follicles. The encapsulated follicular variant of PTC is the most common subtype, but it can be a difficult diagnosis with considerable interobserver variability. This form very rarely metastasizes to lymph nodes (5%), a rate similar to follicular adenomas/carcinomas. In contrast, the more aggressive infiltrative follicular variant of PTC presents with lymph node metastases in 65% of patients, a rate more similar to classic PTC. The follicular variant of PTC has been shown to harbor RAS mutations with a very low incidence of BRAF mutation, similar to follicular adenomas/carcinomas.

**Objective:** To determine whether the mutation profile of follicular variant of PTC is different among encapsulated and infiltrative subtypes.

**Methods:** All clinical cases of thyroid carcinoma, including consultation files, were blindly reviewed by 2 pathologists and classified as follicular variant if 99% of the neoplasm was composed of follicles lined by cells with well-developed characteristic nuclear features of PTC in at least 60% of the tumor. These were designated as encapsulated if surrounded by a fibrous capsule and infiltrative if partially or totally unencapsulated with tongues of tumor infiltrating normal thyroid. Clinicopathological features were collected and compared to genotyping by mass spectrometry and RET/PTC and PAX8/PPARgamma status by PCR.

**Results:** 47 cases of follicular variant of PTC (28 encapsulated and 19 infiltrative subtypes) were included in the study. Patients with encapsulated tumors had a significantly lower rate of extrathyroid extension, positive margins, and lymph node involvement than those with infiltrative tumors. Genotyping abnormalities were found in 39% of encapsulated tumors and in 47% of infiltrative tumors. RAS mutations were found in 10 of 28 encapsulated tumors (36%) and in 2 of 19 infiltrative tumors (11%). BRAF mutations were found in none of the encapsulated tumors but in 5 of 19 infiltrative tumors (26%). PAX8/PPARgamma was rearranged in 1 encapsulated tumor, and RET/PTC recombination was found in 1 infiltrative tumor.

**Conclusions:** Encapsulated follicular variant of PTC has a high rate of RAS mutations similar to that of follicular adenomas/carcinomas, whose behavior it reflects. In contrast, infiltrative follicular variant of PTC has a higher rate of BRAF mutations similar to that of classic PTC, whose behavior it reflects.

**Reviewer’s Comments:** Given the diagnostic difficulty in classifying some thyroid lesions, we may begin to see reliance on molecular genotyping for diagnosis and proper prognostication. (Reviewer—Stacey E. Mills, MD).

© 2010, Oakstone Medical Publishing

Keywords: Papillary Carcinoma, Follicular Variant, Molecular Genotyping

Print Tag: Refer to original journal article
Can We Do Better Than the BRSTC's Category ‘Atypical Follicular Cells’?

Should "Atypical Follicular Cells" in Thyroid Fine-Needle Aspirates Be Subclassified?
Renshaw AA:

Cancer Cytopathol 2010; 118 (August 25): 186-189

Certain thyroid fine-needle aspiration cases interpreted as atypical follicular cells may have a higher risk of malignancy than other cases within this group.

Objective: To examine the risk of malignancy within subgroups of "atypical follicular cells of undetermined significance" in the Bethesda System for Reporting Thyroid Cytopathology (BSRTC).

Background: The recent BSRTC was developed to standardize terminology used in the interpretation of thyroid fine-needle aspiration (FNA) specimens. In particular, this classification system was designed to incorporate the risk of malignancy for each diagnostic category. A new category, "atypical follicular cells" (AFC), was reported to have 5% to 15% risk of malignancy. The current recommendation for follow-up of these patients is repeat FNA. In this study, the author subclassifies AFC cases into 4 groups and evaluates the risk of malignancy in each subgroup.

Methods: All thyroid FNAs over a 13-year period were reclassified according to current BSRTC. Cases classified as AFC were then divided into 4 subgroups based on morphology. Group 1 cases, "atypical cells, rule out papillary carcinoma," typically had a small number of cells with some features of papillary thyroid carcinoma. Group 2 cases, "atypical cells, rule out Hürthle cell neoplasm," were typically low-cellularity aspirates but with exclusively Hürthle cells. Group 3 cases, "atypical cells, rule out a follicular neoplasm," had a mixed macro- and microfollicular pattern. Group 4 cases, "atypical cells, not otherwise specified," were a heterogeneous group without specific features of groups 1 to 3. Histologic follow-up from subsequent resections was used as the gold standard for malignancy and correlated with cytologic results.

Results: Of >7,000 thyroid FNAs during this period, 14% were classified as AFC. A total of 204 cases of AFC had a subsequent surgical resection for comparison, of which 25% were malignant. Risk of malignancy for group 1 (AFC, rule out papillary carcinoma) was 38%, which was significantly higher than the other subgroups. Risk of malignancy for group 2 (AFC, rule out Hürthle cell neoplasm) was 7%, which was significantly lower than the other subgroups. Risk of malignancy for groups 3 and 4 were not significantly different from overall risk of malignancy.

Conclusions: Certain thyroid FNA cases interpreted as AFC may have a higher risk of malignancy than other cases within this group. In particular, cases with focal features of papillary thyroid carcinoma appear to have an increased risk of malignancy, and identification of this subset may be helpful for clinical management.

Reviewer's Comments: Prior to use of the BSRTC, we used the category "atypical cells, cannot exclude papillary thyroid carcinoma," which is very similar to the AFC subgroup "rule out papillary carcinoma." Internal review of these cases showed an even higher risk of malignancy than found in this study. In future iterations of the BSRTC, "AFC, rule out papillary carcinoma" may become a separate category. (Reviewer-Deborah J. Chute, MD).

© 2010, Oakstone Medical Publishing

Keywords: Atypical Follicular Cells, Neoplasia, Resection, Cytology, Fine-Needle Aspiration

Print Tag: Refer to original journal article
A new BRAF inhibitor, called PLX4032, provides complete or partial tumor regression among most patients with metastatic melanoma whose tumors harbor the V600E mutation.

**Background:** Approximately 50% of melanomas carry an activating mutation in the BRAF gene, and >90% of these mutations result from a substitution of glutamic acid for valine at amino acid 600 (V600E). This mutation leads to activation of the gene product and downstream activation of the mitogen-activated protein (MAP) kinase pathway. Currently, high-dose interleukin-2 and dacarbazine are 2 treatments approved by the Food and Drug Administration; each is associated with a response rate of approximately 15%. A newer drug, called PLX4032 (Plexxikon, Roche Pharmaceuticals), has been shown to inhibit BRAF kinase activity, to inhibit MAP kinase signaling, and to block proliferation of cells that harbor BRAF mutations.

**Objective:** To define the safety and pharmacokinetic profile of PLX4032 for the treatment of metastatic melanoma, to determine the maximum dose that may be given for such treatment, and to determine response and progression rates of patients with tumors showing the V600E BRAF mutation who receive the maximal treatment dose.

**Methods:** The authors first conducted a multicenter, phase 1, dose-escalation trial of PLX4032 in 55 patients, 49 of whom had melanoma. This was followed by an extension phase in 32 additional patients with metastatic melanoma whose tumors carried the V600E BRAF mutation. This second phase attempted to determine the maximum dose that could be given without causing adverse effects. Patients received PLX4032 twice daily until disease progression was detected. Study assessments included standardized safety evaluations, adverse event recording, CT studies (8-week intervals), pharmacokinetic assessments, and positron-emission tomography scanning for selected patients. In some patients, tumor biopsy was performed before and during treatment for confirmation of BRAF inhibition using immunohistochemical staining for phosphorylated extracellular signal-regulated kinase (ERK) (a key part of the MAP kinase signaling pathway), cyclin D1, and the proliferation marker Ki-67.

**Results:** The dose recommendation for the initial phase was 960 mg twice daily, with subsequent dose increases limited by the presence of fatigue, rash, and arthralgia. Among 16 patients in the initial phase whose tumors carried the V600E BRAF mutation, 1 showed a complete response and 10 showed a partial response. Among 32 patients in the dose-extension phase, 2 showed a complete response and 24 showed a partial response. Approximate median progression-free survival among all patients exceeded 7 months.

**Conclusions:** PLX4032 treatment for metastatic melanoma in patients with the BRAF V600E mutation is associated with complete or partial tumor regression in most patients.

**Reviewer's Comments:** Pathologists should be aware of this medication and its promise as a melanoma treatment. From a practical standpoint, pathologists may be needed to assess for the presence of the V600E mutation prior to treatment and to quantify tumor response to therapy. (Reviewer-T. David Bourne, MD).

© 2010, Oakstone Medical Publishing

Keywords: Melanoma, Metastases, PLX4032 Therapy, BRAF Mutations

Print Tag: Refer to original journal article
Better imaging techniques allow for identification of more potentially neoplastic disease of the pancreas.

**Background:** Better imaging techniques and more widespread use of imaging have led to increased detection of pancreatic cysts. Some of these cysts represent intraductal papillary mucinous neoplasms or mucinous cystic neoplasms, and many of these are resected in an attempt to cure low-stage cancers or to keep malignancy from developing. T2-weighted magnetic resonance imaging (MRI) is superior for the detection and identification of fluid-filled structures and, thus, cysts.

**Objective:** To determine the prevalence of pancreatic cysts within the population by evaluating MRIs in patients who have undergone imaging for non-pancreatic disease.

**Methods:** All MRIs seen at a single institution over a year were reviewed. Cases were included if the entire pancreas was evaluated. Only imaging performed for patients not suspected of having pancreatic disease was included. All cystic lesions were identified by 2 radiologists. Number and diameter, as well as other characteristics, were recorded. Basic demographic data were also recorded.

**Results:** 616 patients met criteria for inclusion. Mean age was 54 years, and about 60% of patients were women. The prevalence of pancreatic cysts increased with age. Less than 1% of patients aged <40 years had cysts, 20% of those aged 60 to 69 years had cysts, and 40% of those aged >90 years had cysts. Diameter of the largest cyst also increased with age, as did the mean number of cysts per patient. About half of incidental cysts were present in the head or uncinate process of the pancreas. Only 30% of cysts had been originally documented in the radiology reports. Slightly >10% were considered complex or connected to the main duct, each. Of patients who underwent additional imaging for other reasons, about 15% showed some growth of their pancreatic cysts. In one quarter of patients, the cysts were not seen on repeat imaging.

**Conclusions:** Overall, >13% of patients can be found to have pancreatic cysts on MRI performed for reasons not related to pancreatic disease. The percentage increases with age.

**Reviewer’s Comments:** This report demonstrates one of the difficulties faced with better imaging studies. The work-up of these cysts and the benefit of that work-up deserve careful scrutiny. (Reviewer-Edward B. Stelow, MD).

© 2010, Oakstone Medical Publishing

Keywords: Pancreas, Cysts, MRI, Incidence

Print Tag: Refer to original journal article
A survey of laboratory practices and procedures for ABO typing samples provides significant opportunity for improvement and reduction of error.

**Background:** Mistransfusion of red blood cell products is not an uncommon event, with nearly 20% attributed to patient misidentification and/or sample mislabeling errors prior to receipt in the laboratory. This results in ABO incompatibility transfusion rates greater than that of infectious disease transmission from hepatitis B virus, hepatitis C virus, or human immunodeficiency virus. Because of the morbidity and rare mortality associated with ABO incompatibility transfusions, benchmarks for performance should be established to provide guidelines for quality improvement.

**Objective:** To survey clinical laboratories for ABO typing policies with correlation to rates of mislabeled samples or wrong blood in tube (WBIT).

**Methods:** Participants from 122 clinical laboratories prospectively reviewed all ABO typing samples to determine the number received and/or rejected for being incorrectly labeled over a 30-day period. In addition, correlation with historical ABO typing was recorded for the same 30-day period as well as for a retrospective 12-month review. Laboratory policies and procedures were collected for correlation to results.

**Results:** The aggregate mislabeled sample rate was 1.2%, and the aggregate WBIT rate was 0.04%. Higher mislabeled rates were associated with allowing nonlaboratory staff collecting and labeling samples, the percentage of samples collected and labeled by nonlaboratory staff, the institution allowing removal of armbands during admission, and the institution requiring new sample submission if patient’s name is changed/updated during admission. Lower mislabeled rates were associated with requiring the patient location to be confirmed with patient identification before outpatient collection, verifying date of birth, patient location required on outpatient sample labels, sex required on outpatient label or inpatient test requisition, and date of birth required on inpatient test requisition. Higher rates of WBIT were associated with nonlaboratory staff collecting and labeling sample and having a specific policy for replacing armbands that have been removed. Lower rates of WBIT were associated with requiring the phlebotomist’s identification on the inpatient sample labels and date of birth required on inpatient test requisition.

**Conclusions:** Obvious areas of improvement for decreasing mislabeled samples and WBIT for ABO testing include increasing the usage of laboratory-trained phlebotomists, strict adherence to patient identification procedures at sample collection and during administration of products, avoiding accumulation of unused sample labels, and careful patient identification at registration and throughout inpatient stay by armbands.

**Reviewer’s Comments:** Other recommendations included requiring 2 separate samples for ABO typing in patients without historical data, but this utilizes additional resources. (Reviewer-Mary T. Galgano, MD).

© 2010, Oakstone Medical Publishing

Keywords: Blood Bank, Safety Practices

Print Tag: Refer to original journal article
Researchers Study Risk of Transfusing Antigen-Incompatible Blood in the ER

Risk of Hemolytic Transfusion Reactions Following Emergency-Release RBC Transfusion.

Goodell PP, Uhl L, et al:


There is a low, but real, risk of transfusing antigen-incompatible blood in the emergency setting.

**Background:** In emergent situations, it is sometimes necessary to issue group O red blood cells (RBCs). This avoids ABO incompatibility; however, there are other clinically significant alloantibodies that may lead to antibody-mediated hemolytic transfusion reactions (HTRs). These are commonly screened for during the type and screen. Studies have estimated that the rate of alloimmunization ranges from 0.5% to 4.0% in the majority of patients admitted to the emergency room (ER), thus predicting a low risk for transfusion reactions in these situations.

**Objective:** To examine the frequency of a positive antibody detection in ER RBC recipients, those receiving antigen incompatible blood, and risk of a subsequent HTR.

**Methods:** This was a 2-year retrospective study in which recipients who received emergency release RBC units in the ER were identified. If the patient was a female aged <50 years, group O, Rh-negative units were issued. Males and females aged >50 years were given group O, Rh-positive RBCs. Blood bank and clinical records were reviewed.

**Results:** Just over 1000 ER RBC transfusions issued to 262 recipients (265 ER events or episodes) were analyzed. Most recipients received 1.0 to 4.0 units, with an average of 3.8. The 2 most common indications were trauma and gastrointestinal bleeding. In 29 of 265 ER episodes, there was a positive antibody detection identified, 17 of which were clinically significant. Three patients had multiple alloantibodies. Of 17 recipients, 7 patients were transfused a total of 15 antigen-incompatible blood. In 6 of these patients, no HTRs were reported, and a review of the chart indicated no symptoms or signs thereof. A 68-year-old male who presented with gastrointestinal bleeding and had a history of prior transfusion received 1 unit in the ER and 4 units after transfer. No acute reactions were noted, but testing ultimately revealed anti-c, Jka, and E. The transfused unit was c antigen-positive, and E negative (Jka testing was unable to be performed). Approximately 36 hours later, hemolysis labs showed significant elevations in lactate dehydrogenase and total bilirubin and a decreased haptoglobin. It should be noted that a pretransfusion specimen in this patient was positive for DAT, so there was likely an element of delayed hemolysis from his prior transfusion.

**Conclusions:** There is a low, but real, risk of transfusing antigen-incompatible blood in the emergency setting before completion of the routing blood bank testing. This may lead to a non-ABO alloantibody-mediated HTR.

**Reviewer's Comments:** This study provides data to what is already practiced in the emergency setting, but it definitely highlights the risk of transfusing antigen-incompatible blood. What I think is even more practically important is how to manage the patient with known alloantibodies in the emergency setting. (Reviewer-William A. Kanner, MD).

© 2010, Oakstone Medical Publishing

Keywords: Transfusion, Hemolytic Transfusion Reaction

Print Tag: Refer to original journal article
MDM2 Amplification Predicts Behavior of Lipomatous Tumors

Molecular Testing for Lipomatous Tumors: Critical Analysis and Test Recommendations Based on the Analysis of 405 Extremity-Based Tumors.

Am J Surg Pathol 2010; 34 (September): 1304-1311

MDM2 amplification detected by fluorescence in situ hybridization is helpful for classifying large lipomatous tumors.

Background: Lipomatous tumors are the most common mesenchymal tumors. Lipomas are obviously the most common of these lesions. Occasionally, lipomas can be difficult to distinguish from well-differentiated liposarcomas, also known as atypical lipomatous tumors. Lipomas are typified by rearrangements of the chromatin remodeling gene HMG2 at chromosome 12q15, whereas well-differentiated liposarcomas have amplified sequences derived from chromosome bands at 12q13-15, usually in the form of giant marker and ring chromosomes. A number of genes are included here, including MDM2.

Objective: To evaluate the clinicopathologic features of a large cohort of molecularly classified lipomatous tumors.

Methods: 459 cases of lipomatous tumors were used that had been seen over a 10-year period at a single institution. All had been treated by complete excision or resection. No retroperitoneal tumors were included. Only lipomas, intramuscular lipomas, and well-differentiated liposarcomas were included in the study. All slides were reviewed, and tumors were reclassified based on histologic features. Fluorescence in situ hybridization was performed to identify amplification of CPM and MDM2. Tumors with >10% of cells showing amplification were considered positive for amplification. Follow-up information was pursued.

Results: Of those cases with material for molecular analysis, there were 324 classified as lipomas, 29 as intramuscular lipomas, and 52 as well-differentiated liposarcomas. All CPM-amplified cases were also MDM2 amplified. Using amplification as the gold standard for classification, there were 322 lipomas and 35 intramuscular lipomas. Approximately 20% of tumors originally classified as well-differentiated liposarcomas were reclassified as benign lipomas. None of these tumors recurred. Two percent of tumors originally classified as benign were reclassified as sarcomas; 2 of 7 such tumors recurred. No patient died due to disease in this study. The local recurrence rates based on molecular classification were 1%, 12%, and 44% for lipomas, intramuscular lipomas, and well-differentiated liposarcomas, respectively. Tumor type and type of resection were predictive of recurrence.

Conclusions: The authors suggest that molecular testing is not needed for all lipomatous tumors. They suggest it be reserved for recurring tumors, tumors with questionable cytologic atypia, and those >15 cm in size.

Reviewer's Comments: In this study, the authors tended to overdiagnose well-differentiated liposarcomas rather than underdiagnose them when using histology alone. Molecular testing appears to be very helpful for predicting recurrence. (Reviewer: Edward B. Stelow, MD).

© 2010, Oakstone Medical Publishing

Keywords: Lipoma, Liposarcoma, MDM2, CPM, Recurrence

Print Tag: Refer to original journal article
Clear cell meningiomas are negative for renal cell carcinoma antigen and show only focal (if any) staining for CD10 and carbonic anhydrase 9 stains.

**Background:** Clear cell meningioma (CCM) is a relatively rare subtype that has a variable component of cells with abundant clear cytoplasm due to glycogen accumulation. This subtype is important to identify, because it has an increased risk of recurrence compared to typical meningiomas. Most of the time, some part of the tumor shows classical features of meningioma and the diagnosis is not difficult. On small biopsies, however, CCM can mimic metastatic clear cell renal cell carcinoma (ccRCC). In this study, the authors evaluate the utility of immunohistochemistry with carbonic anhydrase 9 (CA9), CD10, and renal cell carcinoma antigen (RCC) to differentiate between CCM and ccRCC.

**Objective:** To identify markers helpful in distinguishing CCM from metastatic ccRCC.

**Methods:** 18 cases of CCM and 26 cases of ccRCC (14 primary, 12 metastatic tumors) were included in the study. The percentage of clear cells was quantified in each case of CCM. All CCMs and ccRCC were immunohistochemically stained with antibodies to CA9, CD10, and RCC. The percentage of positive cells in each tumor was semiquantitated as non, 1% to 5%, 5% to 25%, 26% to 50%, 51% to 75%, and >75%.

**Results:** Clear cell change comprised between 10% and 100% of the CCM tumor (mean, 41%). CA9 immunostaining was observed in 94% of ccRCCs compared to 40% of CCMs. Staining in ccRCCs was widespread (typically present in >50% of cells); however, in the CCMs, staining was focal and typically in <5% of cells. CD10 immunostaining was observed in 100% of ccRCCs compared to 28% of CCMs; again, the staining was widespread in most ccRCCs and focal in CCMs. Finally, RCC immunostaining was observed in 36% of ccRCCs and in no cases of CCM.

**Conclusions:** Immunohistochemical staining with antibodies to CA9, CD10, and RCC are potentially useful in differentiating CCM from metastatic ccRCC. In particular, any case with positive RCC staining should raise strong concern for metastatic renal cell carcinoma, as well as cases with diffuse (>50% of cells) staining for CD10 and/or CA9.

**Reviewer's Comments:** This article highlights an uncommon but potentially critical mimic of ccRCC in the CNS. Luckily, CCMs usually show areas of typical meningioma, but this pitfall would most likely occur in patients who undergo small initial diagnostic biopsies. It is in this setting that immunohistochemistry for CD10 and RCC would likely provide the most benefit. (Reviewer-Deborah J. Chute, MD).

© 2010, Oakstone Medical Publishing

Keywords: Clear Cell Meningioma, Metastatic Renal Cell Carcinoma, Immunohistochemistry

Print Tag: Refer to original journal article
Can Galectin-1 Help Diagnose Chondroblastic Osteosarcoma?

Galectin-1 Is a Powerful Marker to Distinguish Chondroblastic Osteosarcoma and Conventional Chondrosarcoma.

Gomez-Brouchet A, Mourcin F, et al:

Hum Pathol 2010; 41 (September): 1220-1230

Galectin-1 immunostains are positive in chondroblastic osteosarcoma but not positive in conventional chondrosarcoma.

Background: The most common primary tumors of bone are osteosarcoma and chondrosarcoma. Although these tumors are typically easily distinguished on the basis of histology and patient age, there is some overlap, particularly in cases of chondroblastic osteosarcoma. Unfortunately, there currently is no diagnostic marker to distinguish between these 2 tumors, except for the presence of osteoid production, which frequently may be missed on a small biopsy. Because therapy for these tumors is significantly different, an additional marker of osteoblastic lineage would be very helpful in the preoperative planning of these patients.

Objective: To determine the utility of galectin-1 (GAL1) immunohistochemistry in differentiating chondrosarcoma from chondroblastic osteosarcoma.

Methods: 165 osseous tumors (87 osteosarcomas, 78 chondrosarcomas) were used to construct a tissue microarray. Of the osteosarcomas, 25 were chondroblastic type with only focal osteoid production. Each case was stained for GAL1 on 3 separate tumor cores, along with 7 benign osteoblastic proliferations. Cytoplasmic GAL1 immunohistochemical staining was semiquantitatively and qualitatively estimated. In 4 cases (2 chondrosarcomas, 2 chondroblastic osteosarcomas), Western blotting was performed to confirm the level of GAL1 protein expression.

Results: GAL1 immunostaining was intense and diffuse in benign osteoblastic proliferations. Conventional chondrosarcomas were almost always negative for GAL1 or had only focal staining (95%), whereas the majority of osteosarcomas (including chondroblastic osteosarcomas) showed moderate to intense staining in the majority of cells (54%). Western blotting confirmed high expression of GAL1 in osteosarcomas and no significant expression in chondrosarcomas. Four cases of chondrosarcoma showed high expression of GAL1; this was only in areas of de-differentiation and not in the lower-grade component of the tumor. When using a cutoff of >25% of cells staining and/or moderate to intense staining of the tumor cells as a criteria for a diagnosis of osteosarcoma, the sensitivity and specificity of GAL1 were 72% and 95%, respectively.

Conclusions: GAL1 immunohistochemistry is a powerful diagnostic tool in the differentiation of chondroblastic osteosarcoma from conventional chondrosarcoma. Particularly in patients with bone tumor biopsies showing chondroid differentiation, GAL1 may be useful in the diagnosis and selection of appropriate treatment for these patients.

Reviewer's Comments: GAL-1 promises to be a very useful tool in bone tumor pathology; however, it is not only a marker of osteosarcoma. GAL1 expression has been demonstrated in a wide variety of normal tissues and cancers, including papillary thyroid carcinoma, breast cancer, colon cancer, and endothelial cells. Caution should be used when interpreting GAL1 staining outside of the setting of bone tumors with chondroid differentiation. (Reviewer-Deborah J. Chute, MD).

© 2010, Oakstone Medical Publishing

Keywords: Osteosarcoma, Galectin-1, Chondrosarcoma, Chondroblastic Osteosarcoma

Print Tag: Refer to original journal article
What Are the Antibodies of Choice in Diagnosis of Gastrointestinal Stromal Tumors?

DOG1 and CD117 Are the Antibodies of Choice in the Diagnosis of Gastrointestinal Stromal Tumours.

Novelli M, Rossi S, et al:

Histopathology 2010; 57 (August): 259-270

DOG1 is a recently commercially available antibody. Combined CD117 and DOG1 positivity is sufficient to confirm the diagnosis of gastrointestinal stromal tumor in a majority of suspected cases.

Background: The diagnosis and classification of mesenchymal tumors of the gastrointestinal tract were greatly facilitated by the discovery, in 1998, that most gastrointestinal stromal tumors (GISTs) have mutations in the receptor tyrosine kinase gene KIT and that the overexpressed KIT protein (CD117) may be detected by immunohistochemistry. About 5% to 10% of GISTs, however, fail to overexpress CD117 and instead show mutations in a related receptor tyrosine kinase gene platelet-derived growth factor alpha (PDGFRA). Since the widespread adoption of CD117 in clinical laboratories, additional antibodies have been suggested as possible aids in GIST diagnosis. These include PDGFRA, nestin, CD171, protein kinase C-theta (PKC-theta), and the recently available “discovered on GIST-1” (DOG1).

Objective: To assess the quality of staining, sensitivity, specificity, and overall utility of various antibodies used to diagnose GIST.

Methods: 542 GISTs (187 whole-section samples, 355 microarray samples) and a smaller number of gastrointestinal mesenchymal tumors and soft tissue sarcomas were retrieved and submitted for immunohistochemical staining using a panel of antibodies (CD117, DOG1, PKC-theta, nestin, CD34, smooth muscle actin [SMA], desmin, S100, and CD171). Scoring was independently performed by 2 gastrointestinal pathologists. Tumors were considered positive when there was either strong (widespread or patchy) or diffuse (>50% of tumor cells) weak staining above background levels.

Results: For GIST diagnosis, the most sensitive and specific antibodies were CD117 and DOG1. Although sensitive, PKC-theta and nestin were less specific, since they also stained other spindle-cell tumors. CD34 showed significantly less sensitivity than many of the tested markers. Desmin, SMA, and S100 were helpful in excluding other spindle-cell tumors in the differential diagnosis of GIST.

Conclusions: Combined CD117 and DOG1 positivity is sufficient to confirm the diagnosis of GIST in a majority of suspected cases.

Reviewer’s Comments: DOG1 has recently become commercially available. It stands for “discovered on GIST-1,” and the recognized epitope appears on most GISTs, regardless of mutations status. Other studies have reported a sensitivity for GIST of at least 99% when DOG1 and CD117 are combined. (Reviewer-T. David Bourne, MD).

© 2010, Oakstone Medical Publishing

Keywords: Gastrointestinal Stromal Tumor, Immunohistochemistry, DOG1, CD117

Print Tag: Refer to original journal article
Researchers Study Angiogenic Cytokine Levels in AL Amyloidosis

High Levels of Serum Angiogenic Growth Factors in Patients With AL Amyloidosis: Comparisons With Normal Individuals and Multiple Myeloma Patients.
Kastritis E, Roussou M, et al:
Br J Haematol 2010; 150 (September): 587-591

In addition to serum free light chain assessment, angiogenic cytokine levels have been studied in patients with AL amyloidosis, and they appear significantly elevated compared with normal individuals and patients with multiple myeloma.

Background: Patients with primary systemic light chain (AL) amyloidosis have widespread deposition of amyloid fibrils throughout the major organ systems of the body, resulting in severe tissue damage and organ dysfunction. It is thought that interactions between the light chain-producing plasma cell clone and bone marrow may affect the course of disease progression. Since angiogenesis has been shown to play a role in progression of multiple myeloma, it may also affect the progression of AL-type amyloidosis. One way to assess the degree of angiogenic activity is to measure angiogenic cytokine levels in the serum.

Objective: To measure the levels of various angiogenic cytokines in the serum of patients with AL amyloidosis in order to determine whether these levels correlate with disease features, degree of organ involvement, or clinical outcome.

Methods: Using an enzyme-linked immunosorbent assay, serum levels of angiopoietin-1, angiopoietin-2, vascular endothelial growth factor (VEGF), angiogenin, and basic fibroblast growth factor (bFGF) were measured in 82 patients with AL amyloidosis, 35 patients with newly diagnosed and untreated multiple myeloma, and 35 age-matched healthy controls. In addition, serum free light chains and N-terminal fragment of pro B-type natriuretic peptide were measured.

Results: Angiopoietin-1, VEGF, bFGF, and angiogenin were all significantly higher in AL amyloidosis patients than in normal controls and myeloma patients. Levels of angiopoietin-2 correlated with various measures of cardiac dysfunction. None of the serum markers, however, were prognostically significant.

Conclusions: Angiogenic cytokine levels are significantly elevated in patients with AL-type amyloidosis compared with normal individuals and patients with multiple myeloma. Although the precise mechanism is unclear, possible reasons for the increase include a compensatory response to organ dysfunction or a direct toxic effect of amyloid fibrils or light chains.

Reviewer's Comments: Serum free light chain testing has greatly influenced the diagnosis and monitoring of patients with various plasma cell-related disorders. Further studies may eventually support use of angiogenic serum marker testing as a way to further stratify patients in terms of disease risk. (Reviewer-T. David Bourne, MD).

© 2010, Oakstone Medical Publishing

Keywords: AL Amyloidosis, Angiogenic Cytokines

Print Tag: Refer to original journal article
Multilocular Cystic RCC Frequently Demonstrates Deletion of Chromosome 3p

*Multilocular Cystic Renal Cell Carcinoma Is a Subtype of Clear Cell Renal Cell Carcinoma.*

Halat S, Eble JN, et al:

*Mod Pathol* 2010; 23 (July): 931-936

---

Multilocular renal cell carcinoma (RCC) is a subtype of clear cell RCC, based on similar chromosome 3p deletion status.

**Background:** Renal cell carcinoma uncommonly presents as a multilocular cystic tumor. The 2004 WHO classifies the multilocular cystic variant as a subtype of clear cell renal cell carcinoma (RCC), but its good prognosis has caused debate over this classification. Chromosome 3p deletion is a consistent finding in clear cell RCC and is considered a hallmark cytogenetic abnormality.

**Objective:** To compare incidence of chromosome 3p deletion in multilocular cystic RCC with low-grade clear cell RCC.

**Methods:** 19 cases of multilocular cystic RCC were collected using established WHO criteria, which included a cystic tumor with thin septa containing clusters of clear cells having a nuclear grade of 1 or 2 that do not expand the septa. None of the patients had a known genetic syndrome. Also collected for comparison were 19 Fuhrman nuclear grade 1 and 2 clear cell RCCs. Fluorescence in situ hybridization for a chromosome 3 probe was performed on tissue blocks. A total of 100 to 150 tumor cell nuclei were scored for signals, and normal renal cortex served as a control.

**Results:** Multilocular cystic RCCs had a similar size range and male-to-female ratio as the low-grade clear cell RCCs. Of the multilocular RCCs, 74% were Fuhrman nuclear grade 1, and 26% were nuclear grade 2. Of the clear cell RCCs, 11% were grade 1 and 88% were grade 2. A total of 14 of 19 multilocular cystic RCCs (74%) and 17 of 19 clear cell RCCs (89%) had chromosome 3p deletion. This difference was not statistically significant.

**Conclusions:** Multilocular cystic RCC are low-grade and low-stage carcinomas with frequent deletion of chromosome 3p, supporting the hypothesis that they are a subtype of clear cell RCC.

**Reviewer's Comments:** The multilocular cystic RCCs are almost always confined to the kidney and cured by surgery, thus representing a distinct subtype of RCCs. (Reviewer-Mary T. Galgano, MD).

© 2010, Oakstone Medical Publishing

Keywords: Cystic Renal Cell Carcinoma, Multilocular Subtype

Print Tag: Refer to original journal article
CD10 and Myxofibrosarcoma -- Why It Matters

CD10-Positive Myxofibrosarcomas: A Pitfall in the Differential Diagnosis of Atypical Fibroxanthoma.
Clarke LE, Frauenhoffer E, et al:
J Cutan Pathol 2010; 37 (July): 737-743

Consider myxofibrosarcoma in a cutaneous mesenchymal tumor with CD10 staining.

Background: CD10 is an immunohistochemical marker (IHC) that stains numerous normal and neoplastic tissues; however, it is best noted in the dermatopathology literature for its use in marking atypical fibroxanthomas (AFX). The differential diagnosis with AFX includes other spindle cell lesions, such as desmoplastic melanoma, spindle cell squamous cell carcinoma, and leiomyosarcoma. The authors of this article have found that myxofibrosarcoma mimics AFX clinically and histopathologically and also stains for CD10.

Objective: To evaluate CD10 IHC in a variety of mesenchymal neoplasms using a tissue microarray.

Methods: A tissue microarray was constructed that contained a variety of mesenchymal neoplasms, with a total of 114 specimens. This included 36 adipose tumors, 38 fibrocytic/fibroblastic tumors, and 40 fibrohistiocytic tumors. CD10 staining was performed with appropriate controls. Scoring was ultimately categorized from 0 (none) to 3+ (strong and diffuse).

Results: In all, 45% of lesions stained (2+ to 3+) with CD10, including diffuse and strong staining with all 7 AFX cases. Seven of 10 myxofibrosarcomas stained strongly and diffusely. Other notable tumors demonstrating positivity with CD10 included fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma protuberans, and dermatofibromas/fibrous histiocytomas. Expression was generally limited in the adipose tumors, but some liposarcomas did stain with moderate intensity.

Conclusions: Many studies have demonstrated the usefulness of CD10 in AFX; however, these authors have systematically studied CD10 expression in a variety of tumors (outside of the well-studied differential diagnosis mentioned above) that may mimic AFX. In this study, myxofibrosarcomas and MFH demonstrated strong and diffuse staining with CD10. It should be noted that some consider AFX to be a superficial variant of MFH, and, historically, myxofibrosarcoma was considered part of the same spectrum. Myxofibrosarcoma is frequently present in the skin and can mimic AFX, especially the myxoid variant of AFX. The clinical presentations, however, are different. Myxofibrosarcomas usually occur on extremities or limb girdle as opposed to sun-damaged skin on the head and neck with AFX cases. Most of the other cases noted in this study are easily differentiated from AFX.

Reviewer's Comments: CD10 is a commonly used marker and has found a major role in spindle cell lesions of the skin. I would emphasize that CD10 stains a lot of tumors, thus, histologic impression and clinical history are of utmost importance. Furthermore, and especially with a tumor such as AFX, I would prefer to see strong and diffuse staining to consider the tumor to be positive with CD10. (Reviewer-William A. Kanner, MD).

© 2010, Oakstone Medical Publishing

Keywords: CD10, Atypical Fibroxanthoma, Myxofibrosarcoma

Print Tag: Refer to original journal article
Transfusion of bacterially contaminated platelets may have a low clinical impact in patients already on antibiotic therapy.

**Objective:** To assess the clinical impact on patients transfused with bacterially contaminated platelets.

**Background:** Current estimates are that the bacterial contamination rate is 1 in 1000 to 2000 platelet units. Interestingly, the outcome of patients transfused with contaminated units ranges from no clinical effects to a septic shock picture. A recent estimate of mortality from contaminated platelets is approximately 1 in every 800,000 transfusions. The most common source of contamination is the donor, due to skin flora contamination during collection, with the most common organisms being coagulase-negative staphylococci. The challenge is that platelets are stored under conditions that facilitate bacterial growth (constant agitation at room temperature). Thus, this is why platelets are only stored for up to 5 days, and the blood bank must have a method in place to detect bacterial contamination.

**Methods:** In this retrospective review for a period of 1 year, each case in which a report of bacterial contamination of platelets was issued was reviewed. The method of bacterial detection was innoculating samples into aerobic standard Bactec (Becton Dickinson Diagnostic Instrument System, Sparks, MD) bottles that were read continuously for 24 hours. A Gram stain was performed on positive bottles and subsequently subcultured. Medical records for patients who received contaminated units were reviewed. Finally, statistical analysis was performed.

**Results:** During this time, the contamination rate was 1 in 320 apheresis platelets and 1 in 312 pooled whole blood platelets. In total, 71 patients received platelet transfusions that were contaminated by bacteria. Acute myelogenous leukemia was the most common type of cancer for which patients were undergoing treatment. Essentially all cultured organisms were gram-positive (only 1 was gram-negative [*Enterobacter cloacae*]). The vast majority of cultured organisms were coagulase-negative staphylococci, with a minor component of alpha-hemolytic streptococci. In 1 case, *Staphylococcus aureus* was cultured. Only 1 patient had symptoms, which were limited to a temperature increase of 1°C (the unit was contaminated with coagulase-negative staphylococci). In addition, no deaths were reported. Most patients were already on antibiotics, and one third of patients had WBC counts <1.0 x 10^9 /L.

**Conclusions:** The clinical impact of transfusing bacterially contaminated platelets was minimal in this study. Most organisms isolated consisted of gram-positive bacteria, predominantly coagulase-negative staphylococci, likely from donor skin contamination.

**Reviewer’s Comments:** As the blood bank fellow this year, the risk of bacterial contamination with platelets is a consistent topic discussed during rounds. I found this paper to be reassuring about the clinical impact of transfusing platelets given the risk of bacterial contamination. We must, however, keep in light that these were cancer patients, many of whom were already on antibiotics. (Reviewer-William A. Kanner, MD).

© 2010, Oakstone Medical Publishing

Keywords: Platelets, Transfusion, Bacterial Contamination

Print Tag: Refer to original journal article
Researchers Study MYC Translocation in Plasmablastic Lymphomas

Plasmablastic Lymphoma With MYC Translocation: Evidence for a Common Pathway in the Generation of Plasmablastic Features.

Taddesse-Heath L, Meloni-Ehrig A, et al:
Mod Pathol 2010; 23 (July): 991-999

Plasmablastic lymphoma and plasmablastic transformation of plasma cell myeloma can have considerable overlap, including translocation of MYC.

Background: Plasmablastic lymphoma is an aggressive lymphoma frequently described in patients with HIV or in other extranodal sites, such as mucosal-associated tissues. The lymphoma is characteristically composed of large cells with plasmacytic differentiation and a high proliferation rate. Although these features overlap with the plasmablastic transformation of multiple myeloma, they typically do not include the clinicopathologic elements of plasma cell myelomas, such as lytic bone lesions and a monoclonal paraproteinemia. In addition, plasmablastic lymphomas have been described to have a stronger association with Epstein-Barr virus (EBV), except in the setting of HIV infection.

Objective: To present cases of plasmablastic lymphoma with features overlapping with multiple myeloma occurring in patients with HIV.

Methods: 6 cases of HIV-associated plasmablastic lymphoma were retrieved from the files of a single hospital. Of these, 4 were selected due to unusual clinical features and MYC translocation. Immunohistochemistry, in situ hybridization, cytogenetics, and break-apart fluorescent in situ hybridization were performed. Clinical charts were reviewed.

Results: All 6 patients were HIV positive and male. Of the 6 patients, 4 had MYC translocation and disseminated disease with nodal, extranodal, and soft tissue involvement. Those with gastrointestinal involvement had extensive involvement requiring resection to relieve obstruction. Of these 4, 3 had clinical features of plasma cell myeloma, including monoclonal serum immunoglobulins and/or lytic bone lesions. Complex cytogenetic abnormalities were also noted in these 3 cases. Lymphoma cells were CD138 and/or CD38 positive with generally weak or negative B-cell markers (CD79a, CD20). Partial positivity for CD56 and CD10 was noted in 2 of 4 cases. Proliferation rate ranged from 60% to 100%, corresponding to decreasing numbers of mature plasma cells noted. All 4 cases were EBV positive by in situ hybridization.

Conclusions: Plasmablastic lymphoma and plasmablastic transformation of a low-grade plasma cell neoplasm can have overlapping clinical and immunophenotypic features. Both are associated with MYC translocation, which may be responsible for the plasmablastic morphology and aggressive behavior.

Reviewer's Comments: These cases demonstrate the overlap between the 2 plasmablastic entities, but the de novo presentation of disease without a concurrent low-grade plasma cell neoplasm favors the interpretation of a plasmablastic lymphoma. (Reviewer-Mary T. Galgano, MD).

© 2010, Oakstone Medical Publishing

Keywords: Plasmablastic Lymphoma, Plasmablastic Myeloma

Print Tag: Refer to original journal article
Smoking Increases One's Risk for Esophageal Adenocarcinoma

Cigarette Smoking and Adenocarcinomas of the Esophagus and Esophagogastric Junction: A Pooled Analysis From the International BEACON Consortium.

Cook MB, Kamangar F, et al:
J Natl Cancer Inst 2010; 102 (September 8): 1344-1353

Background: Smoking is a major risk factor for development of many cancers. Although its role in the development of esophageal squamous cell carcinoma is clear, its role in the development of esophageal adenocarcinoma and adenocarcinoma of the gastroesophageal junction is less well understood. Previous studies have typically been limited in their ability to assess differences by tumor site, sex, dose–response, and cigarette smoking cessation.

Objective: To investigate these less well-understood aspects of the relationship between smoking and esophageal adenocarcinoma.

Methods: Primary data from 10 population-based studies and 2 cohort studies from the Barrett’s Esophagus and Esophageal Adenocarcinoma Consortium were used. Tumors were classified as esophageal or of the gastroesophageal junction. Nearly 10,000 control subjects were included. Associations between development of adenocarcinoma and duration of smoking and its cessation were assessed. Other variables studied included type of cigarette, age, sex, body-mass index, education, and presence of gastroesophageal reflux.

Results: There were approximately 1500 cases of both esophageal and gastroesophageal junction adenocarcinoma. There were roughly 5 times more men than women included in the study. Strong associations were present between smoking and esophageal adenocarcinoma (odds ratio [OR]=1.96), adenocarcinoma of the gastroesophageal junction (OR=2.18), and either adenocarcinoma (OR=2.08). There was an association between pack-years of cigarette smoking and development of adenocarcinoma at both sites. Smoking cessation decreased the risk for adenocarcinoma, and a greater duration of cessation was associated with a greater reduction in risk for development of adenocarcinoma. All results were similar for either sex.

Conclusions: Regardless of other factors, cigarette smoking is associated with increased risk for adenocarcinoma of the esophagus and gastroesophageal junction. Smoking cessation should be encouraged, especially in patients with other risk factors for development of adenocarcinomas of the esophagus and gastroesophageal junction, as it is associated with decreasing the risk for development of these cancers.

Reviewer's Comments: This huge analysis helps to work out some of the less-understood aspects of the relationship between smoking and development of adenocarcinoma of the esophagus. These studies are helpful, because the incidence of these tumors continues to rise in the West. (Reviewer-Eduard B. Stelow, MD).

© 2010, Oakstone Medical Publishing

Keywords: Adenocarcinoma, Esophagus, Gastroesophageal Junction, Smoking

Print Tag: Refer to original journal article
Recent Study Raises Questions About How We Investigate Cancer Risk in Families

Effects of Prostate-Specific Antigen Testing on Familial Prostate Cancer Risk Estimates.

Bratt O, Garmo H, et al:

J Natl Cancer Inst 2010; 102 (September 8): 1336-1343

Siblings of patients with prostate cancer are at greatest risk for diagnosis of prostate cancer within 1 year of their siblings’ diagnoses.

**Background:** Age and ethnicity are major risk factors for development of adenocarcinoma of the prostate. The exact role of genetics is less well understood, although numerous studies have reported a higher incidence of prostate cancer in families of patients who develop prostate cancer. Some have suggested, however, that increased surveillance may be more related to diagnosis of cancer in these patients than actual heritable risk.

**Objective:** To investigate the incidence of prostate cancer among brothers of men with prostate cancer and particular factors that may be associated with increased diagnostic surveillance of these patients.

**Methods:** This study used data garnered for a nationwide database of prostate cancer in Sweden. The authors studied the risk for development of cancer in >20,000 brothers of nearly 15,000 men who had developed prostate cancer. Data gathered included grade and stage of tumors, time of development of cancer in siblings compared to original brothers' diagnoses, geographic and socioeconomic status of patients, and other family history of prostate cancer.

**Results:** Brothers of patients with prostate cancer were at >3 times the risk for development of prostate cancer compared to other men. On average, brothers were age 60 years. Multiple brothers or fathers with cancer increased the risk even more. Risk for diagnosis of early stage tumor was higher than for metastatic tumor. Greatest risk for diagnosis of prostate cancer, especially for low-stage tumors, was present for the first year after diagnosis of cancer in a sibling. Patients of higher socioeconomic status were at increased risk for diagnosis of prostate cancer compared to those of a lower socioeconomic status, especially for early stage tumors.

**Conclusions:** Although men with a family history of prostate cancer are at increased risk for development of cancer, at least some of that risk appears to be related to increased surveillance of those patients.

**Reviewer's Comments:** This study certainly helps to raise some questions about how we investigate cancer risk in families with known cancer histories. Close attention must be paid to the role of patient evaluation in risk for diagnosis of cancer. (Reviewer-Edward B. Stelow, MD).

© 2010, Oakstone Medical Publishing

Keywords: Prostate, Inherit, Adenocarcinoma, Risk Factors

Print Tag: Refer to original journal article