Microcystic urothelial carcinoma is a rare variant of urothelial carcinoma that may be mistaken for cystitis glandularis.

**Background:** Recognizing the microcystic variant of urothelial carcinoma of the bladder may be challenging at times since it may mimic cystitis glandularis, especially in small biopsy samples. Given its rarity, there are limited data regarding the clinical behavior, pathologic features, and immunohistochemical profile of this tumor variant.

**Objective:** To describe the clinical and pathologic features of 20 cases of microcystic urothelial bladder carcinoma.

**Materials/Methods:** This study included transurethral resection of bladder (TURB) and cystectomy specimens from 20 patients. For each case, clinical data and the pathologic material were reviewed. The pathologic features assessed included the histologic type of urothelial carcinoma based on the World Health Organization classification system, the percentage extent of microcystic carcinoma and conventional urothelial carcinoma, depth of invasion, and TNM staging. Immunohistochemical staining was performed using antibodies against MUC1, MUC5AC, CK7, CK20, p63, GATA3, p27, and Ki67.

**Results:** The extent of microcystic component varied from 50% to 100% of the specimens. The cysts were round-oval and of varying sizes, and the periphery of large cysts was frequently punctuated by many smaller cysts. The cysts were lined by urothelial, low columnar cells, or by a single layer of flattened epithelium of low-intermediate nuclear grade. Focal high-grade conventional urothelial carcinoma was present in 8 cases. By immunohistochemistry, there was variable positivity for cytokeratins 7 and 20, MUC1, MUC5AC, p63, and GATA3. Expression of Ki67, p53, and p27 ranged from 20% to 60%, 10% to 40%, and 10% to 30% of cells, respectively. On follow-up, 11 patients died of disease at 11 to 56 months, and 3 patients were alive with disease at 26 to 37 months. Univariate survival analysis showed no differences for microcystic carcinoma versus conventional urothelial carcinoma ($P=0.548$).

**Conclusions:** Microcystic urothelial carcinoma is a rare variant of urothelial carcinoma that may pose diagnostic difficulties, where it may be mistaken for cystitis glandularis. The clinical history, histologic findings, and immunohistochemical profile should help to distinguish it from its mimics. Its clinical aggressiveness seems to be related to higher stage at diagnosis.

**Reviewer’s Comments:** In addition to cystitis glandularis, microcystic urothelial carcinoma may also be confused with adenocarcinoma of the bladder in small biopsy samples. (Reviewer-T. David Bourne, MD).
Distinguishing Hemophagocytic Lymphohistiocytosis From Other Medical Conditions

Marrow Assessment for Hemophagocytic Lymphohistiocytosis Demonstrates Poor Correlation With Disease Probability.

Ho C, Yao X, et al:

Am J Clin Pathol 2014; 141 (January): 62-71

Enumeration of hemophagocytic histiocytes in bone marrow aspirates or core biopsy sections does not contribute to the distinction of hemophagocytic lymphohistiocytosis from other medical conditions.

**Background:** The diagnosis of hemophagocytic lymphohistiocytosis (HLH) requires either molecular evidence for specific genetic defects of primary disease or clinical evidence for 5 of the following 8 features of secondary (acquired) disease: fever; splenomegaly; peripheral cytopenias; hypertriglyceridemia or hypofibrinogenemia; tissue hemophagocytosis; diminished NK-cell activity; elevated serum ferritin; or elevated soluble CD25. Bone marrow biopsy is typically performed, but there is no evidence for a threshold level of marrow hemophagocytosis that accurately distinguishes HLH from other medical conditions.

**Objective:** To evaluate the morphologic extent of bone marrow hemophagocytosis as a predictor of the clinical syndrome, hemophagocytic lymphohistiocytosis.

**Methods:** Sixty-four adult bone marrow core biopsies and/or aspirates that were either performed for suspicion of acquired HLH or reported to contain hemophagocytosis and with available medical records were identified from the files of the Yale–New Haven Hospital and blindly reviewed.

**Results:** Patient ages ranged from 18 to 87 years (median age, 54 years). Based on clinical assessments including, but not limited, to the eight 2004 criteria for HLH, 45 patients (78%) were clinically determined to be of low suspicion for HLH (HLH-L) and 13 (22%) were considered of high suspicion (HLH-H). The HLH-H group had a much higher median serum ferritin (16,700 μg/L) than compared to the HLH-L group (1870 μg/L; \( P = 0.01 \)), although 14 of the 17 HLH-L patients with measured ferritin levels had levels >500 μg/L. The prevalence of fever (\( P = 0.009 \)), cytopenias (\( P = 0.02 \)), and hypertriglyceridemia and/or hypofibrinogenemia were higher in the HLH-H group, although triglyceride and fibrinogen levels were infrequently measured and of questionable predictive value. In contrast to the predictive significance of these laboratory parameters, there was no significant difference in number of bone marrow hemophagocytic cells between the HLH-H and HLH-L groups. This was true whether hemophagocytic cells were enumerated cytologically per aspirate slide or enumerated as percent of marrow cellularity as highlighted by CD68 staining in paraffin core biopsy sections.

**Conclusions:** Enumeration of hemophagocytic histiocytes in bone marrow aspirates or core biopsy sections does not contribute to the distinction of hemophagocytic lymphohistiocytosis from other medical conditions.

**Reviewer’s Comments:** I strongly agree with the authors that CD68 immunohistochemical staining facilitates recognition and semiquantitation of marrow cytophagocytosis. When provided with clinical information (eg, serum ferritin >15,000, fever, splenomegaly, or cytopenias), hematopathologists can comment that marrow cytophagocytosis supports a clinical diagnosis of hemophagocytic lymphohistiocytosis. But in the absence of strong supporting clinical evidence, hematopathologists should be cautious about suggesting that diagnosis based on marrow morphology alone. (Reviewer-Guy E. Nichols, MD, PhD).

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Keywords: Hemophagocytic, Lymphohistiocytosis, Hemophagocytosis, Bone Marrow

Print Tag: Refer to original journal article
The Point at Which MGUS Is No Longer Uncertainly Significant

**MYC Protein Expression Is Detected in Plasma Cell Myeloma but Not in Monoclonal Gammopathy of Undetermined Significance (MGUS).**

Xiao R, Cerny J, et al:


MYC(+) plasma cells is unusual in monoclonal gammopathy of uncertain significance and favors a more overt plasma cell neoplasm.

**Background:** Monoclonal gammopathy is a clinical symptom of a range of reactive, pre-neoplastic, and earnestly neoplastic disorders. However, diagnosis in many cases can be complicated, although much improved in more recent iterations of the World Health Organization. The diagnostic spectrum includes plasmacytoma, monoclonal gammopathy of uncertain significance (MGUS), smoldering myeloma, and outright plasma cell myeloma (PCM).

**Objective:** To assess the utility of immunohistochemistry (IHC) for MYC(+) plasma cell neoplasms including MGUS and plasma cell myeloma.

**Methods:** Bone marrow cases were obtained from several Massachusetts area institutions including cases with a variety of plasmacytic differentiation including plasmablastic lymphoma (PBL), PCM, MGUS, lymphoplasmacytic lymphoma (LPL), marginal zone lymphoma (MZL), IgG-4–related sclerosing disease and polyclonal plasmacytosis. Cases were subjected to dual IHCs for CD138/MYC.

**Results:** Twenty-six bone marrows with PCM were analyzed with 10% to 90% CD138(+) plasma cells; 84% (22/26) of the PCM bone marrows were MYC(+). Specifically, 8 cases were strong MYC(+) (>70%), 9 cases were intermediate MYC(+) (30% to 70%), and 5 cases were weak MYC(+) (1% to 30%). Twenty-nine bone marrows with MGUS were analyzed with 5% to 10% CD138(+) plasma cells. None of the MGUS bone marrows demonstrated MYC overexpression. Three cases of LPL, 2 cases of MZL, and 3 cases of PBL demonstrated weak MYC(+). Not entirely unexpected, 1 case of PBL demonstrated strong MYC(+) overexpression. In addition, 62.5% (5/8) cases of MGUS progressing to PCM demonstrated MYC(+) overexpression.

**Conclusions:** A majority of cases of MGUS are MYC(-) while cases of PCM are MYC(+); MYC protein expression by IHC may be useful in diagnosing PCM and detecting residual PCM.

**Reviewer’s Comments:** MYC expression is not new in PCM. In fact, the current study and several other studies verify a significantly shorter progression-free survival in MYC(+) PCM. However, it is not time to cast dispersions on those who still count plasma cells. While MYC-expression is useful in a subset of cases, it is important to understand a subset of cases of PCM will never demonstrate MYC(+) and remain clear-cut PCM. In these cases, MYC expression will not be particularly enlightening. *(See images for this review at practicalreviews.com.)* (Reviewer-Frank N. Moore, MD).

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Keywords: MYC, Plasma Cell Myeloma, Monoclonal Gammopathy of Uncertain Significance

Print Tag: Refer to original journal article
Difficult Breast FNAs -- Helpful Features and Possible Pitfalls

_Inconclusive or Erroneous Fine-Needle Aspirates of Breast With Adequate and Representative Material: A Cytologic/Histologic Study._

Shabb NS, Boulos FI, et al:

_Diagn Cytopathol_ 2014; 42 (May): 405-415

Myoepithelial cells and stripped nuclei may be prominent in FNAs from malignant breast lesions; therefore, caution should be taken when using these features to classify an aspirate as benign.

**Background:** Despite their replacement by core needle biopsies in many settings, fine-needle aspirates (FNAs) are still used for the assessment of palpable breast lesions, particularly in practices where cost minimization is a priority. Most adequately cellular breast aspirates can be accurately classified as benign or malignant by an experienced pathologist; however, a subset evades definitive diagnosis despite adequate cellularity.

**Objective:** To characterize cytologic features that can aid in the classification of difficult breast FNAs.

**Methods:** Cytology smears and subsequent surgical pathology material were reviewed for all erroneous and indeterminate breast FNAs collected at the American University of Beirut Medical Center between 2003 and 2009. Cytology slides were assessed for overall cellularity, nuclear features, size and number of epithelial clusters, honeycombing, myoepithelial cells, stromal fragments, stripped nuclei, and cribriform/tubular/papillary architecture. Each parameter was quantified based on a scale of 0 to 4, and cases were reclassified as: benign; atypical/indeterminate, favor benign; suspicious favor malignant; or malignant.

**Results:** Twenty-four FNAs with surgical follow-up were retrieved; 21 with inconclusive diagnoses and 3 with erroneous diagnoses. Final pathology revealed that the majority (15) were invasive adenocarcinomas (2 cribriform, 4 tubular, 1 lobular, 8 not otherwise specified). There were also 3 papillary tumors, 3 fibroepithelial tumors, 2 cribriform ductal carcinoma in situ, and 1 adenomyoepithelioma. All cases were moderately to highly cellular, and atypia was mild to only focally moderate in all cases. The presence of complex epithelial clusters with cribriform architecture was helpful for cases of cribriform carcinoma, while rigid tubular epithelial structures with abrupt changes in diameter, pointed tips, and abnormal branching were useful for the identification of tubular carcinoma. Cellular stromal fragments were seen in the fibroepithelial tumors, and papillary tumors showed papillary fibrovascular cores with columnar cells. Adenomyoepithelioma was characterized by a biphasic cell population with focal nuclear atypia and intranuclear and cytoplasmic vacuolar inclusions. Importantly, myoepithelial cells were a common feature in malignant tumors, but were not always a reliable benign indicator.

**Conclusions:** Indeterminate breast FNAs are usually attributable to overlap between benign and malignant features, as benign aspirates can show high cellularity and mild to moderate atypia while malignant cases can show an abundance of myoepithelial cells.

**Reviewer's Comments:** Although the authors identified features that could be useful for more definitively classifying some of these cases, none of these features adds significantly to existing criteria and in most instances follow-up biopsy was probably necessary to avoid over- or under calling lesions on aspirate. (See image for this review at practicalreviews.com.) (Reviewer-Anne McGehee Mills, MD).

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Keywords: Fine-Needle Aspiration Cytology, Breast, Grey Zone

Print Tag: Refer to original journal article
It appears that D- patients can be transfused apheresis platelets from D+ donors without risk for alloimmunization.

**Background:** One must not forget that ABH antigens are present on the surface of platelets (PLTs), while Rh antigens are not. However, within a PLT unit, there may be a small component of red blood cells (RBCs), with more red cells present in whole blood derived PLTs compared with apheresis-derived units. Because of many logistical issues associated with PLTs, it is not always possible to offer PLTs derived from a D- donor to a D- recipient, leading to potential Rh alloimmunization. In such instances, RhIG may be offered to prevent alloimmunization.

**Objective:** To examine the rate of Rh alloimmunization in D- recipients receiving only apheresis-derived, leukocyte-reduced, PLTs from D+ donors.

**Methods:** In this retrospective study, the medical records and transfusion data were reviewed for D- patients who received apheresis-derived PLTs from D+ donors.

**Results:** Over the 14-year study period, there were 130 D- patients who received 565 D+ prestorage, leukoreduced, apheresis PLT transfusions after the exclusion criteria were applied. The median time between the last transfusion and last antibody screen was 28 weeks. Approximately 50% of the patients were immunosuppressed and just >50% of all patients received >1 D-incompatible PLT transfusion. Seventy-five percent of the transfusions were ABO compatible/identical. In all, none of the patients developed anti-D.

**Conclusions:** At the current time, there are no clear guidelines regarding whether D- patients receiving D+ apheresis PLTs should receive RhIG to prevent the possibility of alloimmunization. While there are RBCs in such units, the amount is minuscule (<0.001 to 0.00043 mL). Despite this, many institutions still offer RhIG in such situations. This study showed that in appropriately evaluable D- patients who received D+ prestorage leukoreduced apheresis PLTs, none developed anti-D. This study provides data that might indicate there is no need for RhIG immuno prophylaxis in such situations.

**Reviewer's Comments:** One question that is constantly thought about in transfusion medicine is what is the risk of giving RhIG? With intramuscular injections, the most common side effects are injection site reactions, skin rash, body aches, and slight body temperature elevations. The risks can be more serious for IV forms with patients with immune thrombocytopenic purpura and include allergic reaction, hemolysis, acute renal insufficiency, disseminated intravascular coagulation, and death. As all formulations are human derived, there is a remote risk of infection transmission. The cost of RhIG is approximately $80 per vial. (Reviewer-William A. Kanner, MD).

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Keywords: Alloimmunization, RhIG, D Antigen, Platelets, Transfusion

Print Tag: Refer to original journal article
Is There a Best Surgical Pathology Ink?

Variable Fidelity of Tissue-Marking Dyes in Surgical Pathology.

Williams AS, Haché KD:

Histopathology 2014; 64 (May): 896-900

Anatomic pathology laboratories should evaluate the performance of their own tissue inks through routine processing, decalcification, and immunohistochemistry protocols.

**Background:** Since pathology specimens often contain surgical resection margins that must be carefully identified grossly and microscopically, various methods of coloring tissue margins have been devised. The most frequent method involves "painting" such margins of interest with colored tissue dyes or inks. Unfortunately, the colored material is sometimes difficult to visualize in the colored tissue during microscopic examination. To date, the color endurance and fidelity of such dyes and inks have not been carefully studied.

**Objective:** To evaluate the performance characteristics of various commercial tissue-marking dyes (TMDs) and artists' inks following routine tissue processing, immunohistochemistry (IHC), and decalcification protocols.

**Methods:** Commercially available TMDs in 7 colors from 2 manufacturers and acrylic artists' inks were obtained. The TMDs were from Cancer Diagnostics Inc. (CDI) and Bradley Products Inc. (Davidson Marking System-DMS). Artists' acrylic ink was obtained from Daler-Rowney USA. Excess nondiagnostic surgical pathology tissue was procured, and the dyes and inks were systematically applied. The tissue was then routinely processed or submitted for a period of decalcification. The presence and color endurance of each dye or ink were then assessed on microscopic slides using standard H&E-stained slides or following IHC staining.

**Results:** The most reliable colors for routine tissue processing, regardless of manufacturer, were black, blue, green, and violet. Less reliability was seen with red, orange, and yellow pigments, especially with artists' inks. For TMDs, there was loss of color following decalcification and IHC for 2 colors (blue and violet) from a single manufacturer (DMS). One manufacturer (CDI), however, showed excellent color endurance and fidelity under all tested conditions. Although a formal cost analysis was not performed, TMDs are often more expensive for routine use compared to artists' inks. Fortunately, the tested artists' inks showed appropriate color endurance after routine processing, decalcification, and IHC.

**Conclusions:** Various TMDs may lose or change color during special tissue processing. This previously unreported artifact may lead to potentially serious errors in the reporting and assessment of margin status. Each laboratory should evaluate its own inking protocol through routine processing, decalcification, and after IHC to ensure color endurance and fidelity.

**Reviewer's Comments:** If you have or begin having problems identifying inked margins on your slides at sign-out, you may want to find out what kind of inking method your lab uses and make suggestions accordingly. (Reviewer-T. David Bourne, MD).

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Keywords: Gross Examination, Margin Inking, Staining, Specimen Handling, Surgical Pathology

Print Tag: Refer to original journal article
What Mutations Drive Majority of JAK2 V617F-Negative Myeloproliferative Neoplasms?

Somatic CALR Mutations in Myeloproliferative Neoplasms With Nonmutated JAK2.

Nangalia J, Massie CE, et al:


Gene mutations in exon 9 of calreticulin (CALR) are present in the majority of myeloproliferative neoplasms that are wild-type for JAK2 and MPL.

Background: Among the 4 most common subtypes of myeloproliferative neoplasia, BCR-ABL translocation is pathognomonic for chronic myeloid leukemia and JAK2 V617F mutation is found in 95% of polycythemia vera and roughly 50% each of essential thrombocythemia and primary myelofibrosis. Infrequently, JAK2 exon 12 mutations are found in JAK2 V617F-negative polycythemia vera and thrombopoietin receptor (MPL) mutations in a few cases of JAK2 V617F-negative essential thrombocythemia and primary myelofibrosis. What mutation(s) drive the majority of JAK2 V617F-negative myeloproliferative neoplasms?

Objective: To identify carcinogenic mutations of myeloproliferative neoplasms with wild-type (nonmutated) JAK2.

Methods: Massive parallel sequencing was performed on matched tumor and constitutional DNA from 151 patients with myeloproliferative neoplasms.

Results: Among 151 patients with myeloproliferative neoplasia, 150 demonstrated 1498 somatic mutations. The most frequently mutated gene was JAK2 with demonstration of JAK2 V617F in 48 of 48 (100%) polycythemia veras, 35 of 62 (56%) essential thrombocythemias, and 27 of 39 (69%) of myelofibrosis. The next most frequently mutated gene was calreticulin (CALR), a previously unrecognized oncogene that showed insertions or deletions in exon 9 in 26 of 31 essential thrombocythemias or myelofibrosis cases that were nonmutated for JAK2 and for MPL. In contrast, there were no CALR mutations in 120 cases of JAK2-mutated or MPL-mutated myeloproliferative neoplasia. Overall, 97% (146 of 151) of myeloproliferative neoplasms demonstrated mutually exclusive mutations in JAK2, MPL, or CALR. CALR mutations were identified in 8% (10 of 120) myelodysplastic syndromes but in no control tissues, lymphomas or solid tumors.

Conclusions: Gene mutations in exon 9 of CALR are present in the majority of myeloproliferative neoplasms that are wild-type for JAK2 and MPL.

Reviewer's Comments: This discovery of a role for CALR in myeloproliferative neoplasia is of similar magnitude to the discovery of JAK2 V617F mutations in 2005. Prior to that, BCR-ABL was the only known specific mutation in myeloproliferative neoplasia. In the near future, an algorithmic or multiplexed approach to JAK2 and CALR mutation analysis, perhaps with infrequent MPL testing, may be very useful for distinguishing early stages of myeloproliferative neoplasia from benign mimics (eg, JAK2-wild type essential thrombocythemia from reactive thrombocytosis). (Reviewer-Guy E. Nichols, MD, PhD).

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Keywords: Myeloproliferative Neoplasia, JAK2V617F, Polycythemia Vera, MPL, CALR

Print Tag: Refer to original journal article
Calreticulin is a useful marker for essential thrombocythemia and primary myelofibrosis (ET/PMF) with JAK-2, MPL, and CALR mutations identified in most cases of ET/PMF.

**Background:** The discovery of calreticulin (CALR) mutations was described in a previous review. As mentioned before, this exciting discovery has allowed for increasing sensitivity and accuracy in the difficult diagnostic space of JAK-2(-) and MPL(-) myeloproliferative neoplasms (MPN), most specifically essential thrombocythemia (ET) and primary myelofibrosis (PMF). Furthermore, the discovery of CSF3R has also refined a less frequent diagnostic dilemma distinction between chronic neutrophilic leukemia (CNL) and reactive, clonal, or atypical forms of non-CNL MPNs. While CSF3R mutations are an exciting development, the current review is limited to CALR.

**Objective:** The current study offers a good review CALR and CSF3R mutations and proposes their inclusion in the forthcoming WHO classification of ET/PMF and CNL, respectively.

**Methods:** The authors review several studies describing CALR and CSF3R while offering support for inclusion in the forthcoming WHO classification of MPNs.

**Results:** The authors note the importance of JAK-2 in the MPN diagnostic rubric and make a similar case for CALR. CALR mutations are proposed to be included as a molecular marker of clonality along-side JAK-2 and MPL mutations within the “major diagnostic criteria” for ET and PMF.

**Conclusions:** CALR mutations are found in a significant number of ET and PMF cases and warrant their inclusion as major diagnostic criteria, such as JAK-2 and MPL, mutations in the forthcoming WHO classification of MPNs.

**Reviewer’s Comments:** Using JAK-2 as a prototype, it is easy to foresee inclusions of CALR in the forthcoming WHO classification for MPNs. Furthermore, just as is the case for JAK-2, discovery of targeted CALR therapeutics is probably not far away. Together JAK-2, MPL and CALR mutations account for a majority of MPN cases including ET and PMF. However, these discoveries only lessen the burden of cases without a clonal molecular marker. Depending on your personal feelings regarding bone marrow examination, the good/bad news is that morphologic examination of bone marrow is still necessary in the diagnosis of MPN. (Reviewer-Frank N. Moore, MD).

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**Keywords:** CALR, CSF3R, Myeloproliferative, WHO, Neutrophilic

**Print Tag:** Refer to original journal article
Can Endometrioid Carcinoma Progress to Undifferentiated Carcinoma?

Molecular Characterization of Undifferentiated Carcinoma Associated With Endometrioid Carcinoma.

Kuhn E, Ayhan A, et al:


Undifferentiated carcinomas occurring in juxtaposition with endometrioid carcinomas likely arise from the endometrioid component due to an accumulation of molecular defects.

**Background:** Uterine and ovarian undifferentiated carcinomas (UCs) are highly aggressive tumors often found in conjunction with conventional low-grade endometrioid carcinomas (EMCs). This frequent association suggests that UC may arise from EMC, but molecular studies supporting this potential pathogenesis are lacking. Prior work has shown that UCs often show microsatellite instability, but otherwise, the molecular features of this tumor have not been well characterized.

**Objective:** To investigate the molecular pathogenesis of ovarian and uterine UCs arising in conjunction with low-grade EMCs.

**Methods:** Mutation analysis was performed on paraffin sections from 20 UCs (18 uterine, 2 ovarian), including 12 with an EMC component. Polymerase chain reactions were performed for regions that have frequently been shown to harbor mutations in endometrial carcinomas: CTNNB1 (β-catenin-encoding gene, exon 3), FBXW7 (exons 9 and 10), KRAS (exon 2), PIK3CA (exons 1, 9, and 20), PPP2R1A (exons 5 and 6), and TP53 (exons 4 to 9). Immunohistochemistry for PTEN and β-catenin was also performed.

**Results:** UCs harbored mutations in PIK3CA (50%; 10/20), CTNNB1 (30%; 6/20), TP53 (30%; 6/20), FBXW7 (20%; 4/20), and PPP2R1A (20%; 4/20). All mutations found in EMCs were shared by the concurrent UCs, while 42% (5/12) of UCs with concurrent EMC showed additional mutations in the undifferentiated component. These 5 mutations were comprised of 3 CTNNB1 mutations, 1 PPP2R1A mutation, and 1 TP53 mutation. All 12 matched EMCs and UCs showed concordant PTEN immunostaining; 67% (8/12) showed concordant nuclear β-catenin staining. Three of the 4 cases with discordant β-catenin showed nuclear accumulation in the UC but not the EMC; only 1 case had nuclear staining only in the EMC. Nuclear accumulation of β-catenin was seen in all cases with CTNNB1 mutations.

**Conclusions:** These findings support a clonal relationship between EMCs and associated UCs. The accumulation of alterations in CTNNB1, PPP2R1A, and TP53 may contribute to progression from EMC to UC.

**Reviewer's Comments:** Because CTNNB1, PPP2R1A, and TP53 mutations can be seen in pure, conventional EMC cases as well as UCs, it is hypothesized that their importance in progression to UC is not tied to the specific type of molecular alterations, but to "oncogenic dosage," meaning an accumulation of tumor-promoting effects. (Reviewer-Anne McGehee Mills, MD).

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Keywords: Undifferentiated Carcinoma, Endometrioid Carcinoma, β-Catenin, Progression

Print Tag: Refer to original journal article
There appears to be poor understanding of medical negligence and the single standard of care assumption among pathologists.

**Background:** Medical malpractice exists ideally to provide appropriate compensation for a patient's injury and to act as a strong incentive for physicians to promote safety. This does assume that physicians understand the legal rule of negligence and know the standards of care. These later points have been questioned.

**Objective:** To study how well pathologists understand medical malpractice negligence and standard of care.

**Methods:** A questionnaire was distributed to pathologists in academic and resident positions at certain programs in Texas. The questionnaire consisted of 10 medical malpractice cases, and the responses were directed at examining the defendant pathologist's care in each case as well as to predict the jury's verdict in each case.

**Results:** There were 281 respondents. In total, in only 2 cases did >50% of respondents correctly identify the defendant pathologist's behavior. The highest percentage for correct identification of the pathologist behavior was 60% and the lowest was 18%. Five cases had <50% pathologist concordance with the actual jury verdict (the percentages overall ranged from 18% to 72%).

**Conclusions:** This study attempted to examine the theoretical versus practical aspects of medical malpractice. In this study, there was significant disagreement between the surveyed pathologists and the legally based assessment of pathology care. Thus, there is incomplete understanding of the legal rule of negligence as well as a single acceptable standard of care. Additional education is clearly needed as well as explorations on alternative methods to provide appropriate compensation to injured patients and establish physician accountability.

**Reviewer’s Comments:** The results from this study are not surprising. Most cases do not go to court, and of course, many of these cases (especially the ones that do go to court) are very difficult ones in which there are many factors. The authors of this study included the 10 cases as an appendix, and while space limitations prevent me from including them, I do recommend you reading them if possible. I do have a few things I noted while reviewing them. One is that frozen section and cytology specimens come up frequently. Secondly, and not surprisingly, it often seems there is a breakdown in communication somewhere between pathologist and treating physician that may have changed the situation. (Reviewer-William A. Kanner, MD).

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Keywords: Medical Malpractice, Pathology, Economic Evaluation

Print Tag: Refer to original journal article
Help Decrease Duplicate Test Orders

Duplicate Laboratory Test Reduction Using a Clinical Decision Support Tool.

Procop GW, Yerian LM, et al:

Am J Clin Pathol 2014; 141 (May): 718-723

Using electronic alerts to prevent duplicate tests from being ordered saves money without adversely affecting patient care.

**Background:** Performing unnecessary duplicate laboratory tests increases the cost of health care. Such duplicate testing has other undesirable consequences, including iatrogenic anemia from unnecessary phlebotomy. A potential advantage of implementing an electronic medical record system is the availability of computerized physician order entry (CPOE), which may be used along with various clinical decision support tools (CDST) — especially electronic alerts — to guide physicians regarding appropriate test ordering and use.

**Objective:** To determine the impact on cost and patient safety of electronically blocking the ability of physicians to place selected duplicate test orders.

**Methods:** Using Epic, the computerized medical information system at the Cleveland Clinic, the authors created a so-called “hard stop” CDST consisting of an electronic alert that prevented electronic placement of a duplicate test order for 1259 orderable tests. The alert informed the ordering provider that a duplicate test order was being attempted, that duplicate testing is not usually warranted more than once per day, and that a duplicate order may only be placed by calling the laboratory directly. For convenience, the alert also displayed the most recent test results. Before implementation, feedback was sought from the medical staff, and the CDST was extensively evaluated in a test environment. After implementation, data related to activation of all hard-stop alerts were collected over a 2-year period. Cost savings related to test avoidance included materials and labor only and did not include any cost savings associated with decreased phlebotomy or decreased physician time related to duplicate test review and follow-up. Finally, the authors tracked any untoward patient care events related to the project by using the Safety Event Reporting System (SERS).

**Results:** Use of the CDST resulted in a 2-year cost savings of $183,586 by blocking 11,790 unnecessary duplicate test orders. No untoward effects related to patient safety or care-related outcomes were reported.

**Conclusions:** Using CDSTs that signal and prevent duplicate test orders within an electronic hospital information system can save substantial health care dollars without compromising delivery of patient care.

**Reviewer’s Comments:** Our own hospital began using the Epic system a few years ago, and our laboratory has created a number of ordering alerts to help guide physicians and other providers as they navigate an ever expanding test menu. This has been especially helpful for molecular tests on surgical pathology material. As a practical point, if you decide to implement a similar hard-stop alert preventing placement of any order by a provider, remember to include exclusion codes that may be used internally by laboratory personnel so that duplicate orders may still be placed for issues related to specimen collection and transport. (Reviewer-Stacey E. Mills, MD).

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Keywords: Testing, Clinical Decision Support, Meaningful Use

Print Tag: Refer to original journal article
TERT Promoter Mutations in Meningiomas

High Incidence of Activating TERT Promoter Mutations in Meningiomas Undergoing Malignant Progression.

Goutagny S, Nault JC, et al:

Brain Pathol 2014; 24 (March): 184-189

The incidence of TERT promoter mutations is high in meningiomas that undergo malignant progression.

Background: Meningiomas are the most frequent primary intracranial tumors, representing >33.3% of intracranial neoplasms. While most meningiomas grow slowly over time, some tumors may more rapidly recur after initial resection or undergo malignant transformation. This behavior is reflected in the current World Health Organization (WHO) classification system, which defines 3 tumor grades that are predictive of recurrence risk based on selected histologic features. It has been shown that maintenance of telomere length plays an important role in malignant progression, and mutations in telomerase reverse transcriptase (TERT) have recently been identified in many cancer types.

Objective: To test the hypothesis that TERT promoter mutations are involved in malignant progression of meningiomas.

Methods: Eighty-five meningioma samples from 73 patients were separated into 3 experimental groups. The first group included tumor samples from patients with at least 2 operations, after which there was histologic evidence of tumor progression to a higher grade. The second group included tumor samples from patients whose re-operations were for recurrent tumors showing no evidence of tumor progression to a higher grade. The third group included meningioma samples removed after a single surgery. Each tumor was submitted for TERT promoter mutation analysis.

Results: There was a high incidence of TERT promoter mutations in meningiomas that had undergone malignant progression to a higher WHO grade (28%), and this mutation was seen in both the lower and subsequent higher grade tumors. In contrast, there was a significantly lower incidence of TERT promoter mutations in tumors showing no recurrence or progression. The authors also showed that recurrent tumors without histological progression lacked TERT promoter mutations (n=20). Finally, there was a marked increase in TERT expression in tumors harboring TERT promoter mutations.

Conclusions: TERT promoter mutations appear to play an important role in the malignant progression of meningiomas, and identifying tumors with TERT mutations may help identify patients who are at an increased risk of having tumor recurrence or malignant tumor progression.

Reviewer’s Comments: If validated in a larger patient cohort, I think the most practical use for determining the TERT promoter mutation status of a given meningioma would be its potential use in providing an objective reason to offer post-surgical radiation therapy to selected patients. (Reviewer-T. David Bourne, MD).

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Keywords: Meningiomas, Malignant Progression, TERT Mutations, Neurofibromatosis 2

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What Is the Spectrum of Genetic Change Seen in PCBCL?

Multiple Genetic Alterations in Primary Cutaneous Large B-Cell Lymphoma, Leg Type Support a Common Lymphomagenesis With Activated B-Cell-Like Diffuse Large B-Cell Lymphoma.

Pham-Ledard A, Prochazkova-Carlotti M, et al:

Mod Pathol 2014; 27 (March): 402-411

Primary cutaneous large B-cell lymphoma, leg type demonstrates genetic similarities to nodal-based diffuse large B-cell lymphomas of activated B-cell-type including a high rate of L265P MYD88 mutation.

Background: Primary cutaneous large B-cell lymphoma, leg type (PCBCL) is rare and distinct from other forms of primary cutaneous B-cell lymphoma for its clinical aggressiveness. At the time of presentation, clinicians and pathologists are typically unaware of complete staging information required to distinguish it from systemic large cell lymphoma, and therefore, a conventional large B-cell evaluation is performed. To interpret routine parameters of a cutaneous large B-cell lymphoma evaluation one must know the spectrum of genetic alterations found in PCBCL.

Objective: To assess PCBCL for genetic abnormalities commonly found in other B-cell lymphomas.

Methods: Twenty-three paraffin embedded skin biopsies of PCBCL were retrospectively identified in the files of the University Hospital of Bordeaux and the French study group of cutaneous lymphomas and evaluated by interphase FISH for BCL2, cMYC, BCL6, CDKN2A (p16; 9p21), and BLIMP1 (6q21) gene status and by immunohistochemistry for BCL2, IRF4/MUM1, BCL6, CD10, and cMYC proteins. Cutoffs for immunopositivity were 30% tumor cell staining for all markers except cMYC for which the cutoff was 50%. Evaluation for the L265P MYD88 gene mutation was performed by targeted PCR amplification and Sanger sequencing.

Results: Twenty-two of 23 (96%) PCBCLs demonstrated at least 1 genetic abnormality among evaluated genes BCL2, BCL6, cMYC, CDKN2A, BLIMP1 or MYD88. These included L265P MYD88 mutation in 61%, BLIMP1 (6q21) deletion in 61%, BCL6 rearrangement in 26%, BCL6 (3q) copy number change in 22%, CDKN2A (p16) deletion in 22%, cMYC rearrangement in 13%, and BCL2 rearrangement in 4%. No double or triple hit lymphomas were identified. Only cutaneous ulceration was statistically associated with fatal outcome, which was not the case for any genetic abnormality.

Conclusions: PCBCL demonstrates genetic similarities to nodal-based diffuse large B-cell lymphomas of activated B-cell-type.

Reviewer's Comments: These authors speculate that the high rate of L265P MYD88 mutation suggests potential for NF-kappaB targeted therapies against PCBCL. My primary interest in their observations arises when characterizing a large B cell lymphoma presenting in skin or superficial soft tissue before clinical staging is complete and when the differential includes PCBCL versus systemic lymphoma. For example, detection of a cMYC abnormality favors neither one nor the other. (Reviewer-Guy E. Nichols, MD, PhD).

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Keywords: Diffuse Large B-Cell Lymphoma, MYC, Primary Cutaneous Large B-Cell Lymphoma, Leg Type

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Difficulties of Diagnosing Lymphomas in the Immunocompromised

HHV-8-Positive and EBV-Positive Intravascular Lymphoma: An Unusual Presentation of Extracavitary Primary Effusion Lymphoma.

Crane GM, Ambinder RF, et al:

Am J Surg Pathol 2014; 38 (March): 426-432

Clinical, location/distribution of disease, and immunophenotypes including HHV and EBV are crucial in lymphomas arising in the immunocompromised.

Background: Intravascular large B-cell lymphomas (IVLBCLs) and primary effusion lymphomas (PELs) have been discussed in several previous reviews. However, it is important to point out that lymphomas arising in immunocompromised patients are complicated and not entirely well delineated. In this clinical setting, the disease distribution and associations with human herpes virus type-8 (HHV-8) and Epstein-Barr virus (EBV) heavily influence the diagnosis. However, it is clear that a subset of cases do not classify easily with mass-forming PELs already described.

Objective: To expand the description of PEL to include intravascular PELs.

Methods: A 59-year-old HIV(+) male presented with complaints of diarrhea, weight loss, and cognitive decline. Physical examination was negative for skin lesions or lymphadenopathy. Radiographic studies (CT imaging) identified numerous small subcutaneous nodules within the abdomen and pelvis. Bone marrow biopsy was negative. Fine-needle aspirate of a subcutaneous nodule demonstrated rare atypical cells. Excisional biopsy of subcutaneous nodules demonstrated vessels with organizing thrombi and large atypical cells with prominent nucleoli. Atypical cells were EBV(+), HHV-8(+), MUM-1(+), CD79a weak(+), CD45 weak(+) and CD3 weak(+), and CD4 weak(+). Atypical cells were CD138(-), CD38(-) and otherwise pan B-cell marker(-). Molecular (polymerase chain reaction [PCR]) testing demonstrated polyclonal T-cells and oligoclonal B-cells.

Results: Although the immunophenotypes including HHV(+) and EBV(+) are most consistent with PEL, the exclusive intravascular distribution is unusual. The presence of aberrant T-cell markers has been described in cases of HHV(+) and EBV(+) B-cell lymphomas. While PCR B-cell clonality studies yield only an oligoclonal pattern, recall that PEL is often a lymphoma of low tumor burden and additional evidence supports B-cell lymphomas in immunocompromised patients progressing through polyclonal, oligoclonal, and outright clonal stages.

Conclusions: This case is best classified as a PEL with an intravascular distribution highlighting the multiple parameters necessary in diagnosing lymphomas in immunocompromised patients including clinical, disease distribution, and immunophenotypic information.

Reviewer's Comments: That this case is not an unusual variant of intravascular lymphoma cannot be proven with any dogma. Lymphomas arising in the immunocompromised require a preponderance of evidence including clinical context, disease distribution, and immunophenotype including associations with HHV-8 and EBV. These features must be weighed for the final diagnosis. While the clinical tempo may be rapid in such cases, outside consultation and molecular studies are often necessary when features are less than definitive. (See images for this review at practicalreviews.com.) (Reviewer-Frank N. Moore, MD).

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Keywords: Intravascular Lymphoma, HHV-8, Epstein-Barr Virus, Primary Effusion Lymphoma

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Is It Risky to Spare the Nipple in Mastectomy?

Prophylactic Nipple-Sparing Mastectomy Leaves More Terminal Duct Lobular Units In Situ as Compared With Skin-Sparing Mastectomy.

van Verschuer VMT, van Deurzen CHM, et al:


The nipple-areola complex often contains terminal duct lobular units, calling into question the safety of nipple-sparing mastectomy in high-risk patients.

**Background:** Terminal duct lobular units (TDLUs) are the site-of-origin for both ductal and lobular invasive breast carcinomas. Skin-sparing mastectomy (SSM) has been demonstrated to significantly reduce breast cancer risk in women with heritable breast cancer syndromes, presumably due to near elimination of TDLUs. In this surgery, the nipple-areola complex (NAC) is removed. Nipple-sparing mastectomy (NSM) is an alternative approach that preserves the NAC and its vascular supply; however, the long-term oncologic safety of this procedure has not been demonstrated.

**Objective:** To evaluate mastectomy specimens for the quantity of TDLUs behind the NAC and compare this to the number of TDLUs behind the breast skin flap to assess whether mastectomy techniques that spare the nipple/areola place patients at an increased risk for breast carcinoma.

**Methods:** Women ≥18 years of age who underwent conventional mastectomy or SSM for prophylactic or therapeutic indications were eligible. Cases with malignancy within 1 cm of the nipple and/or skin were excluded from the study. The NAC was dissected away from the rest of the mastectomy in a manner analogous to what would be done in an NSM and then serially sectioned perpendicular to skin. An island of adjacent periareolar skin was sectioned for comparison because this was thought to represent the most TDLU-rich tissue that would remain in a patient after SSM. Slides from NAC and adjacent skin were scanned, and tissue surface areas were measured. TDLUs were then counted and TDLU density (number of units/cm²) was calculated for the NAC and compared to the skin.

**Results:** A total of 105 NACs and adjacent skin specimens from 90 women were evaluated; 61% (64/105) of NACs and 24% (25/105) of skin specimens contained ≥1 TDLU. Twenty-one mastectomies had TDLUs in both the NAC and the skin, 37 had TDLUs in neither area, and 43 had TDLUs only in the NAC. The median number of TDLUs was 2 in the NAC (range, 0 to 186) and 0 in the skin (range, 0 to 48). After adjusting for slide areas, median TDLU density was 0.2/cm² in the NAC (range, 0.0 to 8.5/cm²) versus 0.0 cm² (range, 0.0 to 0.5 cm²) in the skin. Risk factors for the presence of TDLUs in the NAC were younger age (OR, 0.93; 95% CI, 0.89 to 0.98) and parity (≥1 childbirth vs nulliparous; OR, 7.6; 95% CI, 1.8 to 32.3).

**Conclusions:** The TDLU density is higher behind the NAC when compared to adjacent skin; therefore, NSM may be less safe than procedures that spare only the skin envelope.

**Reviewer’s Comments:** Other studies have shown that malignancies that arise after NSM occur in the axillary tail or upper outer breast quadrant, rather than the NAC. Determining the true risk imposed by leaving the NAC in place requires long-term follow-up studies, particularly in high-risk BRCA-mutated patients. (Reviewer-Anne McGehee Mills, MD).

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Keywords: Prophylactic Nipple-Sparing Mastectomy, BRCA1/2, Terminal Duct Lobular Unit

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Acid-fast stains have good sensitivity and high specificity for the detection of mycobacteria in cases of unexplained granulomatous skin reactions.

**Background:** Granulomatous inflammation is commonly encountered in skin biopsies. The difficulty is that the differential diagnosis for such reactions may be broad, including everything from a ruptured epidermal inclusion cyst to mycobacterial infection to sarcoidosis. Without a specific cause, special stains are often performed, and one of the stains most commonly ordered includes an acid-fast stain (AFS). Culture studies for mycobacteria infections may take weeks for final results. PCR has been studied and the studies have shown differing results when compared with special stains.

**Objective:** To examine the utility of ordering acid-fast stains in the setting of granulomatous skin reactions.

**Methods:** This was a retrospective study in which cases of unexplained granulomatous skin reactions were diagnosed and studies with AFS and tissue culture and/or polymerase chain reaction (PCR) studies for mycobacteria were performed. Patients on antibiotic therapy were excluded.

**Results:** Thirty-one cases were identified. There were 8 patients in which AFS was interpreted as either positive or suspicious and culture studies were positive. One of the patients did not have cultures but had a positive PCR study. One patient had an AFS interpretation of occasional positive structures that were suspicious for mycobacteria, and this patient had negative culture and PCR studies. There were no cases with unequivocal AFS positivity and negative cultures. Three cases were negative on AFS but had positive culture studies. Overall, the sensitivity of AFS was 73%, and the specificity was 95%. The positive predictive value was 89%, and the negative predictive value was 86%.

**Conclusions:** This study does show that in the setting of unexplained granulomatous inflammation in the skin, AFS has good sensitivity and high specificity. This supports the common use of this stain in such situations, despite the tediousness of interpreting this stain. Also important is the rapid turnaround time and low cost of this compared to culture and PCR studies.

**Reviewer’s Comments:** Important points in this study are that such stains should be done when the findings are unexplained, such as lack of keratin flakes as may be seen in ruptured epidermal inclusion cysts. It is always important to get a clinical history in such situations when possible. Other stains to consider include periodic acid-Schiff fungal, Grocott’s methenamine silver, and gram stains. Additionally, it is easy to forget to polarize such specimens as that may be helpful. (Reviewer-William A. Kanner, MD).

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Keywords: Mycobacteria, Skin, Acid-Fast Stain

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