Distinguishing Between TTP-HUS and DIC

Platelet Count and Prothrombin Time Help Distinguish Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome From Disseminated Intravascular Coagulation in Adults.

Park YA, Waldrum MR, Marques MB:

Am J Clin Pathol 2010; 133 (March): 460-465

Routine laboratory tests help distinguish between TTP-HUS and DIC.

Background: The microangiopathic hemolytic anemias, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) are life-threatening conditions with significant clinical overlap. Although TTP is classically described by a pentad of signs, the more likely clinical scenario involves a patient with unexplained thrombocytopenia and hemolytic anemia. TTP is often fatal without therapeutic plasma exchange (TPE). Regarding HUS, the tendency is to use the term TTP-HUS and treat with TPE. Acute DIC is the most difficult differential diagnosis to distinguish from TTP-HUS, as it may present with the complete pentad of signs. Testing for TTP-HUS includes ADAMTS13 activity, which should be low in TTP. However, this test is not sensitive enough to identify every patient who will benefit from TPE, and the assay is available primarily in reference laboratories, which precludes appropriate turn-around-times.
Objective: To evaluate which routine laboratory tests could differentiate between TTP-HUS and DIC.
Design: This was a retrospective case-controlled study.
Methods: Each identified patient with TTP-HUS was matched with up to 2 control patients with DIC. All patients had the same admission laboratory tests, which included a CBC, prothrombin time (PT), partial prothrombin time (PTT), D-dimer, creatinine, and LDH. Statistical analysis was then performed.
Results: 27 adults with TTP-HUS and 51 control patients with DIC were identified. On univariate analysis, platelet count, PT, INR, and PTT were all statistically significant (P <0.05) between TTP-HUS and DIC. However, after multivariate analysis, only PT and the degree of thrombocytopenia remained associated with TTP-HUS. A platelet count of <20 x 103/µL and a PT within 5 seconds of the upper limit for the reference interval had a sensitivity of only 52% but a specificity of 92%.
Conclusions: Readily available laboratory tests, especially platelet counts and PT, help differentiate TTP-HUS from DIC in the right clinical scenario, and may help guide proper referral for therapeutic plasma exchange during an acute presentation.
Reviewer's Comments: This article addresses the emergency clinical differential diagnosis between TTP-HUS and DIC and how routine laboratory tests, such as platelet count and PT, may help guide the clinician toward one or the other diagnosis. As described in the article, at the University of Virginia we often test for ADAMTS13 activity in patients suspected of having TTP-HUS. However, we also send this test out to a reference laboratory. Therefore, this is not a test that is able to be used in the acute setting, which has implications as to whether the patient will get therapeutic plasma exchange. (Reviewer-William A. Kanner, MD).

Keywords: TTP-HUS, DIC, PT, Platelets

Print Tag: Refer to original journal article

Increased Daily Screening Equals Reduced Accuracy

Increasing Cytotechnologist Workload Above 100 Slides Per Day Using the ThinPrep Imaging System Leads to Significant Reductions in Screening Accuracy.

Elsheikh TM, Kirkpatrick JL, et al:

Cancer Cytopathol 2010; February 11 (): epub ahead of print

Increasing CT workloads to >100 Pap screens per day cancels out the increased sensitivity gained by using the ThinPrep Imaging System.

Background: Laboratories across the country are attempting to increase productivity in many areas, including gynecologic cytology. The ThinPrep imaging system (TIS) is a Food and Drug Administration (FDA)-approved computer imaging system designed to assist cytotechnologists (CTs) in the primary screening of ThinPrep Papanicolaou (Pap) tests. The TIS was shown to significantly improve detection of abnormal cases. In addition, the FDA approval included a higher screening limit for CTs: 200 TIS-assisted slides a day, compared to 100 a day for manual screening.
Objective: To examine the screening performance of 3 CTs who systematically increased their workload to >100 slides a day using the TIS.
Methods: Over 8 weeks, 3 CTs with variable work experience screened nearly 10,000 Pap smears, all of which were processed using the TIS. Individual CT workloads were assessed, as were total abnormal findings (atypical squamous cells [ASC+]) and high-grade squamous intraepithelial lesion (HSIL) rates. During phase 1, CTs were asked to screen at their usual speed and not change their habits. During phase 2, they were asked to screen as fast as they felt comfortable. During phase 3, they were asked to try and meet a 15% productivity increase in screening over phase 2. All Pap tests underwent 100% rescreening by other CTs not involved in the study.
Results: During the 8 weeks of this trial, there was approximately a 35% increase in average daily productivity. The average number of slides screened per hour increased from 12 to 16. This was achieved by a decrease in the number of cases that underwent full manual review (from 25% to 20%), as well as a decreased amount of time spent reviewing the 22 fields of view per case (from 5 to 3.7 minutes per case). There was a decrease in ASC+ cases detected (from 10.4% to 8.3%) and HSIL detected (from 0.9% to 0.7%). Interviews with the CTs after the study highlighted several negative reactions, including pressure to perform, guilt over reduced patient care, and a need for frequent rests.
Conclusions: An increased CT workload of >100 slides per day with the TIS is accomplished primarily through reducing time spent per case and the percentage of cases that underwent full manual screening, resulting in decreased performance. Screening >100 slides per day appears to proportionally cancel out the increased sensitivity gained by TIS, especially in detecting HSIL lesions.
Reviewer's Comments: It is interesting to note that, in the original FDA clinical trial for TIS, those who reported average daily screening rates in excess of 200 slides worked ≤5 hours, and the rates were extrapolated to 8 hours. It is possible that the performance of these CTs may have decreased when working a full day at that rate. (Reviewer-Deborah J. Chute, MD).

Keywords: Cytopathology, Pap Smear, Workload, ThinPrep, Location-Guided Screening, Imaging System

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Reporting Neuroendocrine Tumors -- What Information Is Needed?

Pathology Reporting of Neuroendocrine Tumors: Application of the Delphic Consensus Process to the Development of a Minimum Pathology Data Set.

Klimstra DS, Modlin IR, et al:

Am J Surg Pathol 2010; 34 (March): 300-313

A number of findings should be included when diagnosing any neuroendocrine epithelial tumor.

Background: Epithelial neuroendocrine tumors are common and can occur throughout most of the epithelial organs in the body. There is a diverse nomenclature for these lesions reflecting the tumors' speculated cell of origin, differentiation, or histologic growth patterns. The World Health Organization has generally adhered to site-specific grading, staging, and classification schemes. Because of the numerous naming systems and lack of consistent grading schema, the authors of this manuscript believe our understanding of the tumors is compromised.
Objective: To develop a "minimal data set" of information that should be included with the reporting of all neuroendocrine epithelial tumors.
Methods: An international panel of "experts" was assembled. A Delphic consensus method was used to determine minimal information that was thought to be necessary when reporting neuroendocrine tumors. Agreement was defined as 80% of the voting members agreeing to a particular issue.
Results: The group did not attempt to identify a single terminological classification system, although it was agreed that the term “carcinoid” is archaic yet entrenched. There was no agreement regarding use of the terms “tumor,” “neoplasm,” and “carcinoma.” Although it was agreed that immunohistochemistry was recommended for the diagnosis of most lesions, it was not mandated. There was agreement that chromogranin and synaptophysin were the only 2 immunohistochemical stains that should be used routinely. Keratin, p53, and peptide hormone immunohistochemistry is generally not needed. For the reporting of resected primary tumors, the following were included within the minimum pathology data set: tumor site, diagnosis, tumor size, presence of unusual histologic features, presence of multicentric disease, grade (with specification of grading system used), the presence of nonischemic necrosis, the presence of nonendocrine components, extent of invasion (differing depending on site of tumor), presence of vascular invasion, presence of perineural invasion, presence and number of lymph nodes with metastatic disease, TNM staging (with specification of staging system used), margin status, and changes seen in apparently non-neoplastic endocrine cells. Immunohistochemistry for endocrine markers and proliferation degree (Ki67 index) were considered optional. The authors also reported minimal pathologic data sets for the reporting of biopsies of primary and metastatic tumors and the reporting of resected metastatic tumors.
Conclusions: While there is disagreement about diagnostic terminology, there is mostly agreement as to what pathologic parameters should be reported when dealing with these tumors. It is hoped that the universal reporting of the suggested parameters will allow for better evaluation of parameters that cannot be agreed upon as important.
Reviewer's Comments: This well-written manuscript contains very lengthy and helpful discussions regarding the reporting and classification of neuroendocrine tumors. Pathologists who encounter these tumors should consider familiarizing themselves with it. (Reviewer-Edward B. Stelow, MD).

Keywords: Neuroendocrine, Reporting, Lung, Gastrointestinal, Pancreas

Print Tag: Refer to original journal article

Prognostic Factors of Vulvar Paget Disease

Paget Disease of the Vulva: A Histologic Study of 56 Cases Correlating Pathologic Features and Disease Course.

Shaco-Levy R, Bean SM, et al:

Int J Gynecol Pathol 2010; 29 (January): 69-78

Paget disease of the vulva frequently recurs, especially after positive surgical margins, but only epidermal acantholysis predicts recurrence with statistical significance.

Background: The predominantly intraepithelial adenocarcinoma of the vulva, so-called Paget disease (PD), has a chronic clinical course. The insidious nature of PD is owed to difficulty in assessing the extent of disease at surgery and its probable multifocal nature. In few cases, an invasive component is recognized, but this and other histologic features have an unknown prognostic significance.
Objective: To characterize a large series of PD to assess pathologic features for correlation to disease course.
Methods: Only patients with a primary cutaneous PD of the vulva were selected, excluding adnexal, urothelial, and rectal carcinomas with an intraepidermal component. Each condition was evaluated for clinicopathologic features with slide review to document growth pattern, adnexal involvement, invasion, pseudo-invasion, disease extent of epidermis, cytologic atypia, gland formation, mitotic activity, signet-ring morphology, epidermal acantholysis, hyperkeratosis, parakeratosis, inflammation, margin status, frozen section results, lymph node status, immunoprofile, and histochemical stain results.
Results: Of the 56 patients identified, the mean age at diagnosis was 69 years, and most patients were Caucasian. The presenting symptom was itching, often with burning. An erythematous, white plaque of the labia majora was noted in most cases. The lesions averaged 5.6 cm, and almost half of the women had bilateral disease. With an average follow-up of 5.6 years, 32% of cases recurred after surgical intervention. Although cases with positive margins tended to recur, epidermal acantholysis was the only associated risk factor with statistical significance; 18% of the women had invasion, but this did not prove to be an adverse prognostic factor. Overall, however, it was noted that these women tended to have more radical surgical intervention. The only death from disease was associated with the deepest invasion (6 mm), but this patient was also noted to have extensive disease. Frozen section analysis did not improve the final margin status on permanent sections, nor did it reduce the recurrence rate. Paget cells were positive for CK7, CEA, and usually mucin, while they were negative for S-100, HMB-45, and Mart-1.
Conclusions: PD commonly recurs after surgery, especially when margins are positive, but only epidermal acantholysis has a statistically significant association with recurrence.
Reviewer's Comments: Invasion of PD was frequently noted in the biopsy with subsequent surgical intervention noted to be more aggressive. That may explain the lack of a significant association with recurrence. Perhaps epidermal acantholysis should be treated with a similar surgical approach to decrease recurrence rates. (Reviewer-Mary T. Galgano, MD).

Keywords: Paget Disease, Vulva

Print Tag: Refer to original journal article

How Many Platelets Does It Take?

Dose of Prophylactic Platelet Transfusions and Prevention of Hemorrhage.

Slichter SJ, Kaufman RM, et al:

N Engl J Med 2010; 362 (February 18): 600-613

While a decreased number of transfused platelets per patient is observed when low doses are given for prophylactic transfusion, an increase in the number of actual transfusions occurs.

Background: Although the optimal number of platelets to administer during prophylactic platelet transfusion remains controversial, a standard dose usually contains between 3.0 x 1011 and 6.0 x 1011 platelets. However, some recently published studies have demonstrated the effectiveness of lower-dose platelet transfusions for the prevention of clinically significant bleeding.
Objective: Among other goals, the authors attempted to determine the effects of platelet dose on clinical signs of bleeding in patients with thrombocytopenia.
Methods: Hospitalized patients who were undergoing bone marrow stem cell transplants, patients with hematologic malignancies, or patients with solid malignancies were randomly assigned to 1 of 3 groups for prophylactic administration of platelet transfusions when morning platelet counts fell below a threshold value of 10,000 per cubic millimeter. The 3 groups were based on low-, medium-, and high-dose platelet administration amounts, which corresponded to 1.1 x 1011, 2.2 x 1011, and 4.4 x 1011 platelets per square meter of body-surface area, respectively. Patients were evaluated for bleeding on a daily basis utilizing information from physical examination, patient interviews, and chart reviews. The primary end point was bleeding of at least grade 2, according to established World Health Organization criteria.
Results: 1351 patients were initially enrolled in the study. The 10,000 platelet count trigger threshold was adhered to on 90%, 92%, and 94% of days in each of the 3 study groups, respectively. Only 7% of patients had a change in the trigger threshold for clinical reasons before the onset of a grade 2 or higher bleeding episode. Of 1272 patients in the study who received at least one platelet transfusion, bleeding of grade 2 or higher was observed in 71% of patients in the low-dose group, 69% of those in the medium-dose group, and 70% of patients in the high-dose group. While the median number of transfused platelets was lower in the low-dose group (9.25 x 1011) compared to the medium-dose group (11.25 x 1011) or high-dose group (19.63 x 1011), the median number of actual transfusions given in the low-dose group (n=5) significantly exceeded the number of transfusions given in the medium-dose group (n=3) and high-dose group (n=3) (P <0.001). As morning platelet counts increased, the percentage of days of clinical bleeding decreased significantly.
Conclusions: While a decreased number of transfused platelets per patient is observed when low doses are given for prophylactic transfusion, an increase in the number of actual transfusions occurs. Importantly, the dose of platelet transfusion has no significant effect on bleeding incidence after a threshold of 10,000 platelets per cubic millimeter or lower is reached.
Reviewer's Comments: As the authors suggest, utilizing a low-dose strategy might save platelet supply, but the number of required transfusions will likely increase. (Reviewer-T. David Bourne, MD).

Keywords: Platelet Transfusion Dosing

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p16 Improves Diagnostic Accuracy of CIN

Conjunctive p16INK4a Testing Significantly Increases Accuracy in Diagnosing High-Grade Cervical Intraepithelial Neoplasia.

Bergeron C, Ordi J, et al:

Am J Clin Pathol 2010; 133 (March): 395-406

The diagnostic accuracy of diagnosing high-grade CIN is increased when p16 immunostaining is added to standard H&E interpretation.

Background: Cervical biopsy and conization specimens are frequently encountered in the daily practice of surgical pathology. Accurate classification of biopsy material into the appropriate diagnostic categories of negative for dysplasia or cervical intraepithelial neoplasia (CIN) (grades 1 to 3) has important implications for directing patient management. Depending on human papillomavirus (HPV) type, current practice usually involves excisional or ablative therapy for high-grade (CIN 2 or 3) lesions, while low-grade lesions may be left untreated. Thus, the goal is to avoid both over-treating false-positive cases and under-treating false-negative ones. Unfortunately, the diagnosis of CIN is associated with moderate interobserver agreement at best—a fact reflected in kappa values ranging from 0.20 to 0.50 in many published studies.
Objective: To determine the value of using p16 immunostaining in conjunction with H&E slide interpretation in the diagnosis of high-grade CIN in biopsy material.
Methods: 12 community-based pathologists rendered independent diagnoses on a series of 500 H&E-stained cervical punch and conization specimens, followed by re-evaluation at least 4 weeks later of the same set of biopsies with the addition of p16 immunostaining. Thus, each of the 12 pathologists rendered 1000 individual diagnoses for the study. The community pathologists were blinded to the gold standard diagnoses and to their original diagnoses. The gold standard diagnoses were established by a panel of 3 expert gynecological pathologists. Results for cases with complete agreement or with 2-of-3 majority consensus review were used as the reference standard. p16 staining was considered "positive" when there was continuous staining of the basal and parabasal cell layers of the squamous epithelium and "negative" when there was only isolated cell staining or positive cell clusters or no immunoreactivity within the epithelium.
Results: By adding p16 immunohistochemical staining to H&E slide evaluation, there was a significant increase in the diagnostic accuracy for detecting high-grade CIN among community pathologists. The mean kappa value increased from 0.566 to 0.749 after the addition of p16 staining. Importantly, the intraobserver agreement for p16 interpretation was high (kappa=0.899).
Conclusions: p16 immunohistochemical staining improves the diagnostic accuracy of cervical biopsy interpretations, thus increasing the likelihood of optimal patient management.
Reviewer's Comments: An obvious strength of this study is its reliance on 12,000 individual biopsy readings. The authors also avoid the so-called incorporation bias by basing the gold standard diagnoses on H&E findings alone. Otherwise, as the authors point out, the test results would be incorporated into the very evidence used to establish the true diagnoses. It is interesting to note, however, that of the 500 original H&E-stained biopsies originally reviewed by the expert panel, there were only 253 cases for which all 3 experts initially agreed. (Reviewer-Stacey E. Mills, MD).

Keywords: CIN, Conjunctive p16 Immunostaining

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How to Respond to Large-Scale Testing Errors

Responding to Large-Scale Testing Errors.

Valenstein PN, Alpern SG, Keren DF:

Am J Clin Pathol 2010; 133 (March): 440-446

There is an orderly way in responding to large-scale testing errors.

Background: The clinical laboratory is susceptible to large-scale testing errors. These errors may affect a large number of laboratory results because of a system defect in high-volume testing. Furthermore, the clinical impact of the error may not be completely understood. With high-volume testing, there is also no time to wait for a root-cause analysis, and the potential damage must be addressed immediately.
Objective: The authors use 2 case studies to illustrate the unique challenges involved with large-scale testing errors. They also point out 9 distinct constituencies that require attention. **Case 1:** At laboratory X, a College of American Pathologists inspector noted that the calculated INR value was 8% greater than the INR reported by the analyzer who had measured the prothrombin time. It was found that an "adjustment ratio" had not been calculated and entered into the analyzer at the time of last calibration. **Case 2:** At laboratory Y, a technologist noted that there was a negative HIV1, HIV2 enzyme-linked immunosorbent assay result in a patient who had tested positive weeks earlier. The samples were positive on retesting, with appropriate controls. The instrument on which the test was run was investigated and found to have a non-dispense event that occurred in about 1 in 400 specimens.
Conclusions: Based on their experience, the authors identified 9 constituencies to be considered: (1) prevent additional errors for patients who are to undergo testing; this must be done immediately by either correcting the underlying error, if known, or by finding alternative testing; (2 and 3) there must be an assessment of the risk of adverse outcome for those tested, and it should also be established who should be notified. Results should also be corrected; (4) test charges should be reversed for tests in question; (5) laboratories are obligated to notify regulators and accreditors when appropriate; (6) although not an obligation, it may be desirable to be prepared for media attention and to address whether there is a risk to public health and safety; (7) alert the vendor to assess if there is a device problem and whether the FDA needs to be notified; (8) although laboratory directors are usually not owners, it is important to notify the organization that owns the laboratory; and (9) although there is no legal requirement to notify those in the lab; this provides transparency, promotes a culture of safety, and encourages bidirectional communication within the lab.
Reviewer's Comments: This is an important article that addresses an issue that can be quite involved and stressful. It is essential for the laboratory to maintain the appropriate quality of care. (Reviewer-William A. Kanner, MD).

Keywords: Large-Scale Testing Errors, Clinical Laboratory

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DAP Predicts Aggressive Disease

Any Proportion of Ductal Adenocarcinoma in Radical Prostatectomy Specimens Predicts Extraprostatic Extension.

Samaratunga H, Duffy D, et al:

Hum Pathol 2010; 41 (February): 281-285

Ductal adenocarcinoma of the prostate should be considered a high-grade malignancy, as it is frequently associated with increased tumor stage.

Background: Ductal adenocarcinoma of the prostate gland (DAP) is a distinct variant of prostatic carcinoma characterized by tall columnar cells and pseudostratified nuclei (previously termed endometrioid adenocarcinoma of the prostate). The prognostic significance of this variant is debated, but many authors have suggested that DAP is associated with more aggressive tumors with advanced stage.
Objective: In this study, the authors examine the relationship of DAP in radical prostatectomy specimens with extracapsular extension (T3 disease), Gleason score, tumor volume, and PSA level, in comparison to typical acinar adenocarcinomas of the prostate (AA).
Methods: 268 consecutive radical prostatectomy specimens were studied; the prostates were submitted in total and examined for a component of DAP. For each case, the location of the tumor, percentage of DAP (if present), tumor volume, tumor stage, and Gleason score were recorded. Tumors were classified as pT3 if extraprostatic extension or seminal vesicle involvement were present. Clinical data including patient age and serum PSA level were also recorded.
Results: In 34 cases (13%), a component of DAP was present, ranging from 5% to 100% of the tumor (91% had <50% DAP). Only 1 case was comprised of DAP only; the remaining tumors were mixed with AA. There was no significant difference in patient age, serum PSA level, or surgical margin status between tumors with and without DAP. All cases with DAP showed involvement of the peripheral zone; in 46% of cases, the transitional zone was also involved. In comparison, all cases of pure AA involved the peripheral zone, but only 12% involved the transitional zone. Pathologic stage 3 (pT3) disease was present in 73% of tumors with DAP, compared to only 33% of tumors comprised of AA only. Tumors with DAP were also associated with Gleason scores >7 in 65% of cases, compared to only 10% of pure AA. On multivariate analysis, the presence of any proportion of DAP remained a significant predictor of increased tumor stage (pT3).
Conclusions: DAP is more likely than conventional AA to be associated with extraprostatic extension and increased tumor stage. This validates the current recommendation that DAP should be considered a high-grade malignancy and assigned at least Gleason grade 4. Any component of DAP on core biopsy should be reported, regardless of how small.
Reviewer's Comments: DAP in association with AA is more common than previously reported, comprising nearly 13% of tumors. However, DAP in its pure form represents <1% of tumors. Previous studies have shown that the 5-year progression-free survival for prostate tumors with a DAP component is closer to pure AA tumors with a Gleason score of 7 to 8. (Reviewer-Deborah J. Chute, MD).

Keywords: Prostate, Adenocarcinoma, Ductal Adenocarcinoma, Tumor Stage, Gleason Grade

Print Tag: Refer to original journal article

HPV Vaccine Reduces Risk of CIN

Impact of Human Papillomavirus (HPV)-6/11/16/18 Vaccine on All HPV-Associated Genital Diseases in Young Women.

Muñoz N, Kjaer SK, et al:

J Natl Cancer Inst 2010; 102 (March 3): 325-339

The quadrivalent HPV vaccine quickly reduces the number of women who develop CIN and genital warts.

Background: Cervical cancer is the second most common cause of cancer death worldwide in young women. This cancer has been fought in the past primarily with effective screening methods. Recently, the development of human papillomavirus (HPV) vaccines has led to hope for the prevention of even more cervical cancers, especially for populations not able to be screened. Although use of the vaccine has not been of sufficient time to use cancer as an end point, this study looked at a number of end points for patients vaccinated with the quadrivalent HPV virus-like particle (HPV6/11/16/18 vaccine).
Methods: Over 2 years, >17,000 women were enrolled in randomized controlled studies of the HPV6/11/16/18 vaccine. Women who had histories of HPV-related disease or who had >4 sexual partners were generally excluded. End points included cervical intraepithelial neoplasia (CIN), anogenital or vaginal lesions, Pap test abnormalities, and therapeutic procedures for these abnormalities. Patients returned regularly over 4 years for comprehensive examinations and Pap tests.
Results: At day 1 of the studies, nearly one-third of the women tested positive for HPV. The population of women considered to be naïve to HPV infection who were vaccinated showed a 30% reduction in the risk for CIN with a 43% reduction in the development of CIN2 or 3. There was also an 82% reduction in the development of genital warts and a 77% reduction in the development of vulvar intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN) 2 or 3. In the population of women deemed sexually active (that is, not necessarily HPV-naïve at the beginning of the study), there was a 19% reduction in CIN with a 19% reduction in the development of CIN2 or 3. There also was a 63% reduction in the development of genital warts and a 51% reduction in the development of VIN or VaIN 2 or 3. It was estimated that, per 100,000 HPV-naïve women, 710 cases of CIN would be prevented, 1380 Pap test abnormalities would be prevented, and 1020 cases of genital warts and/or VIN/VaIN lesions would be prevented. For the sexually active group, it was estimated that, per 100,000 women, 800 cases of CIN would be prevented, along with 1320 Pap test abnormalities and 830 cases of genital warts and/or VIN/VaIN lesions.
Conclusions: The authors suggest that vaccination with the HPV6/11/16/18 vaccine would rapidly reduce the number of women who develop CIN, genital warts, or VIN/VaIN. Therefore, it would also reduce the number of therapeutic procedures performed.
Reviewer's Comments: The quadrivalent vaccine works well for reducing cervical and other genital disease caused by HPV. It will likely also reduce the number of cancers affecting these sites. (Reviewer-Edward B. Stelow, MD).

Keywords: HPV Vaccine, HPV 16, Genital Warts, CIN

Print Tag: Refer to original journal article

Survival in Low-Stage Ovarian Carcinoma

Tumor Type and Substage Predict Survival in Stage I and II Ovarian Carcinoma: Insights and Implications.

Köbel M, Kalloger SE, et al:

Gynecol Oncol 2010; 116 (January): 50-56

Endometrioid and mucinous ovarian carcinomas presenting with stage Ia and Ib disease have good prognosis.

Background: Studies have previously indicated that tumor grade is an important prognostic factor in stage I ovarian carcinomas. A treatment recommendation at some cancer centers is to not give adjuvant therapy to women with stage Ia, grade 1 ovarian carcinomas and possibly not to women with stage Ib. Others consider that grade 2 tumors should also be included in this low-risk category, but grading has been shown to be unreproducible. In order to define a more reproducible variable on which to risk stratify and base treatment decisions, tumor typing and substaging may be useful.
Objective: To determine whether a population of low-risk patients can be identified with subtyping of ovarian carcinomas.
Participants/Methods: 1326 women were identified as having been treated for stage I-II ovarian carcinoma, but only 652 had pathological material available for slide review. Two pathologists blindly reviewed the slides for tumor type and grade using contemporary criteria. A few were excluded due to reclassification as borderline, metastasis, or rare subtype, leaving 605 cases for evaluation of outcome after standardized treatment primarily consisting of surgery and platinum-based chemotherapy regimens.
Results: The cases were stratified as 31.2% high-grade serous, 30.6% endometrioid, 27.3% clear cell, 8.9% mucinous, and 2% low-grade serous carcinoma. The grading of each tumor was stratified as: 50.2% grade 3; 22.5% grade 2; and 27.1% grade 1. The stage of each patient was stratified as: 20.3% Ia; 2.5% Ib, 26.6% Ic; 1.2% IIa; 9.3% IIb; and 40% IIc. According to treatment guidelines, 39 patients did not receive adjuvant chemotherapy, and the disease-specific survival (DSS) was 97% at 10 years compared to the 70.1% DSS at 10 years for the entire group. No single feature could predict outcome, but multivariate analysis revealed age, ascites, substage, and tumor type as independent prognostic factors. Within the endometrioid and mucinous type tumor, those presenting as stage Ia/b had a DSS 10-year survival of 95%. Clear cell carcinomas presenting as stage Ia/b had better outcome than those with Ic-II, DSS at 10 years of 87% and 66%, respectively). No high-grade serous carcinoma group could be identified with improved prognosis.
Conclusions: Careful tumor typing and substaging of low-stage ovarian carcinoma can provide prognostic information and may influence recommendations for adjuvant chemotherapy.
Reviewer's Comments: Most of us would agree that tumor typing is more reproducible than tumor grading of ovarian carcinomas. However, many of the subtypes have a strong correlation to grade. For example, mucinous tumors are usually low grade, and clear cell carcinoma by definition is high grade. (Reviewer-Mary T. Galgano, MD).

Keywords: Tumor Type, Substage, Survival

Print Tag: Refer to original journal article

How Well Do We Agree?

Small Cell Carcinoma of the Lung and Large Cell Neuroendocrine Carcinoma Interobserver Variability.

den Bakker MA, Willemsen S, et al:

Histopathology 2010; 56 (February): 356-363

There is only fair interobserver agreement among pathologists in diagnosing SCLC and LCNEC.

Background: Traditionally, lung cancer diagnoses are divided between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), since there are important clinical and biological differences between these 2 diagnostic categories. SCLC tends to progress more rapidly and is associated with earlier metastases compared with tumors in the NSCLC group. Therapy considerations also differ, since most SCLCs are treated with etoposide as well as platinum-containing drugs instead of surgery. In recent years, however, a benefit of surgery has been demonstrated in selected patients thought to have limited SCLC disease that is completely resectable. While SCLC represents a prototypical neuroendocrine tumor, members of the NSCLC category (namely large cell neuroendocrine carcinoma [LCNEC]) also share this characteristic differentiation. Since no single histological feature can reliably distinguish SCLC from LCNEC, a combination of morphologic features must be assessed. Unfortunately, this introduces subjectivity into the process of interpretation.
Objectives: To determine the interobserver variation in diagnosing SCLC and LCNEC, thereby testing the hypothesis that these tumor types can be reliably separated using published morphological criteria.
Methods: 9 pathologists who had an interest in pulmonary pathology were asked to select a single representative H&E-stained slide from large biopsy or primary tumor resection specimens of SCLC, LCNEC, or neuroendocrine carcinoma (NEC) from their respective institutions. All cases of LCNEC or NEC required immunohistochemical confirmation of neuroendocrine differentiation. The selected slides were sent to a central facility for relabeling and randomization. The 9 pathologists then scored each case based on the 2004 World Health Organization (WHO) lung tumor classification system.
Results: Among the 170 selected cases, a unanimous diagnosis was rendered in 20 cases (12%) and a consensus diagnosis (at least 5 pathologists agreed) was rendered in 117 cases (69%). No consensus diagnosis was made in 33 cases (19%). There was marked variability among the pathologists' diagnoses, reflected by the fact that the number of cases diagnosed as SCLC ranged from 28.7% to 63.7% of cases. The number of cases diagnosed as LCNEC ranged from 8.2% to 49.7% of cases. The overall agreement among observers was only fair (kappa = 0.40).
Conclusions: There is only fair interobserver agreement among pathologists in diagnosing SCLC and LCNEC. The current WHO criteria leave significant room for subjective interpretation of the morphologic findings.
Reviewer's Comments: The findings of this study were certainly not reassuring. The authors were thus prudent in mentioning the potential value of additional immunohistochemical markers to aid in the diagnosis. (Reviewer-T. David Bourne, MD).

Keywords: Interobserver Diagnostic Agreement, SCLC, LCNEC

Print Tag: Refer to original journal article

Clinicopathologic Feature of DHLs Warrant Recognition as a Single Diagnostic Entity

B-Cell Lymphomas With Concurrent IGH-BCL2 and MYC Rearrangements Are Aggressive Neoplasms With Clinical and Pathologic Features Distinct From Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma.

Snuderl M, Kolman OK, et al:

Am J Surg Pathol 2010; 34 (March): 327-340

Lymphomas with t(14;18) and *MYC* rearrangement are very aggressive.

Background: Immunoglobulin genes are often involved in translocations that occur in B-cell lymphomas. Follicular lymphomas (FLs) most often have the t(14;18)(q32;q21), which juxtaposes *BCL2* and *IGH*. This translocation is also seen in 20% to 30% of diffuse large B-cell lymphomas (DLBCLs). Burkitt lymphoma (BL), on the other hand, is characterized by translocations involving *MYC* at 8q24 that typically pair it with an immunoglobulin gene. *MYC* rearrangements are also found in 5% to 15% of DLBCLs, however. Uncommonly, B-cell lymphomas have both the t(14;18) and *MYC* rearrangement. These lymphomas are highly aggressive and have overlapping features with BL and DLBCL and sometimes even with B-lymphoblastic lymphoma/leukemia (B-LBL). These "double hit" lymphomas (DHLs) have generally been reported only in small series.
Objective: This manuscript reviews the clinicopathologic features of 20 consecutive cases of these seen at a single institution.
Methods: All lymphomas with concurrent t(14;18) and *MYC* rearrangements seen at a single institution over a 5-year period were reviewed. All routine and ancillary pathologic materials were reviewed, and cases were classified as per the current World Health Organization (WHO) classification system. Cases were compared to control BL and DLBCL cases.
Results: There were 20 DHLs from 11 men and 9 women with a median age of 63.5 years. No patients had HIV. Six patients had previously diagnosed grade 1 or 2 FLs. Patients were treated with moderate- or high-intensity regimens, and the majority received rituximab. Only 6 patients were alive after a median follow-up of 7.3 months, 4 of whom remained in complete response. By WHO classification, 12 were considered B-cell lymphomas, unclassifiable, 7 were DLBCLs, and 1 was B-LBL. Of the unclassifiable cases, the morphologic pattern was generally somewhere between that of BL and DLBCL, often appearing more like BL but typically with too little proliferative activity. In 2 of 5 cases that had previous tissue diagnosed as FL, a blastoid morphology was present. By immunohistochemistry, all cases were bcl2 positive. Ninety percent of cases had a germinal center immunophenotype. All cases tested had complex karyotypes. Interestingly, the *MYC* partner was typically IGL. Patients with DHLs had higher serum LDH levels than controls. They typically presented at higher stage and survived for less time.
Conclusions: The authors suggest that the clinicopathologic feature of DHLs warrant recognition as a single diagnostic entity.
Reviewer's Comments: This manuscript presents a large series of an apparently distinct type of B-cell lymphoma. It stresses the importance of ancillary testing, especially cytogenetic analysis, for the correct subclassification of lymphomas. (Reviewer-Edward B. Stelow, MD).

Keywords: B-Cell Lymphoma, Burkitt, Diffuse Large B-Cell

Print Tag: Refer to original journal article

Characteristics of APL at Time of Relapse

Acute Promyelocytic Leukemia at Time of Relapse Commonly Demonstrates Cytogenetic Evidence of Clonal Evolution and Variability in Blast Immunophenotypic Features.

Dimov ND, Medeiros LJ, et al:

Am J Clin Pathol 2010; 133 (March): 484-490

Blast morphology and fusion transcript size in APL at the time of relapse remains stable, but there are changes in the immunophenotype and cytogenetics.

Background: Acute promyelocytic leukemia (APL) represents 10% to 15% of all cases of acute myeloid leukemia (AML), with reports of higher incidence in the pediatric and Latino populations. APL is characterized by the t(15;17)(q22;q12) translocation leading to the novel PML-RARα protein. There are 2 morphologic variants, macroglandular and microglandular, with some differences in immunophenotype between them. Although highly responsive to treatment protocols (90% of patients have a complete response), up to 30% relapse.
Objective: To study the characteristics of relapsed APL patients.
Participants/Methods: The authors performed a retrospective review from a pool of 207 APL patients treated at M.D. Anderson Cancer Center. They compared clinicopathologic, immunophenotypic, molecular, and cytogenetic findings between initial presentation and relapse.
Results: 38 cases were identified (26 males and 12 females, with a mean age of 44 years at initial diagnosis). There were 55 morphologic relapses documented (some cases had >1 relapse). The mean time to first relapse was 20.2 months, and 30 of the 38 cases had relapse only in the bone marrow. In 37 cases, the morphology of the blasts was stable. Only 1 case, which was originally a macroglandular variant, relapsed as a microglandular variant. Only 9 cases had flow for both the initial presentation and relapse, yet 8 of 9 cases demonstrated some immunophenotypic change. The most frequent change was either lost or reduced expression of CD13. Other cases demonstrated a gain of either CD33, CD34, or HLA-DR. Over 50% of the relapsed APL cases demonstrated cytogenetically detectable chromosomal abnormalities in addition to t(15;17). The most frequent abnormalities included chromosomes 3, 8, 7, and 11. Regarding the fusion transcript, in all cases that had comparison between the initial presentation and the relapse, there was no change in the length of this transcript.
Conclusions: Relapse of APL occurred in approximately 20% of the patients in this study. The authors found that the blast morphology and fusion transcript size are usually stable at relapse. However, there were significant immunophenotypic and cytogenetic changes.
Reviewer's Comments: This study addresses important diagnostic considerations in following APL patients since a significant fraction of these patients will have relapse. Importantly, this study did not include information regarding cases in which there was only molecular evidence of relapsed APL. (Reviewer-William A. Kanner, MD).

Keywords: Acute Promyelocytic Leukemia, Relapse, Characteristics

Print Tag: Refer to original journal article

Pathologic Findings in Novel H1N1 Influenza

Pathologic Findings in Novel Influenza A (H1N1) Virus ("Swine Flu") Infection: Contrasting Clinical Manifestations and Lung Pathology in Two Fatal Cases.

Mukhopadhyay S, Philip AT, Stoppacher R:

Am J Clin Pathol 2010; 133 (March): 380-387

Diffuse alveolar disease, which may be accompanied by acute bronchopneumonia, is the predominant pathologic finding in novel influenza A H1N1.

Background: Each of the 3 major genera of influenza virus (A, B, and C) is further subclassified based on the viral proteins hemagglutinin (HA) and neuraminidase (N). Only 3 subtypes of influenza A are circulating in humans, H1N1, H1N2, and H3N2. Novel H1N1 is a combination of 2 types of swine influenza, one of which is a reassortment of human, avian, and swine strains. Novel H1N1 is antigenically and genetically distinct from H1N1. The first cases of what has become novel influenza virus A (H1N1) were reported in March 2009. At the time of this publication, there have been >27,000 cases with 127 deaths in the United States.
Objective: To describe the clinicopathologic findings at autopsy in 2 patients diagnosed with novel H1N1 infection. Case 1 involved a 36-year-old man presented with a 4-day history of cough, fever, and malaise that progressed after treatment with antibiotics. Subsequently, it was learned that his girlfriend's 3 children all had flu-like symptoms (not tested) a week prior to his presentation. His condition worsened despite oseltamivir (Tamiflu), and he died on day 15 of his illness. A nasal swab was confirmed positive for novel H1N1 viral RNA by real-time reverse transcriptase polymerase chain reaction (rRT-PCR). At autopsy, the lungs were congested and heavy (combined weight, 2925 g). Microscopically, the predominant finding was diffuse alveolar disease (DAD), acute stage, with hyaline membrane formation. Also notable was extensive intra-alveolar hemorrhage. Only focal squamous metaplasia was identified in 1 bronchus. Case 2 was that of a 46-year-old homeless woman found unresponsive and on admission was intoxicated and confused. There was concern for aspiration pneumonia and treatment was initiated. However, she rapidly declined and died on day 5. At autopsy, 2 samples of lung and a nasal swab all tested positive for novel H1N1 viral RNA by rRT-PCR. High viral loads were noted. Autopsy findings demonstrated heavy lungs with bilateral pleural effusions. Histologically, the major finding was acute bronchopneumonia with neutrophils filling the alveolar spaces. Gram stain demonstrated Gram-positive cocci. DAD, with hyaline membrane formation, was identified both intermixed and away from the areas of bronchopneumonia.
Conclusions: As with other viral manifestations, DAD is the major histologic finding of novel influenza A H1N1. This has a broad differential diagnosis, and ancillary testing may be indicated. Although necrotizing bronchitis/bronchiolitis and squamous metaplasia are classically associated with influenza pneumonia, neither was prominent in these cases. Finally, acute bronchopneumonia may coexist or mask an underlying process.
Reviewer's Comments: This article supports that the pathologic findings are similar to that of other influenza infections and discusses how the pathologists contributed to final diagnosis in each case (proper autopsy work-up and mindfulness of coexisting conditions). (Reviewer-William A. Kanner, MD).

Keywords: Novel H1N1, Influenza, DAD

Print Tag: Refer to original journal article

Do Cutaneous Head, Neck SCCs Need New Staging System?

N1S3: A Revised Staging System for Head and Neck Cutaneous Squamous Cell Carcinoma With Lymph Node Metastases: Results of 2 Australian Cancer Centers.

Forest V-I, Clark JJ, et al:

Cancer 2010; 116 (March 1): 1298-1304

Parotid region metastases of cutaneous SCC should have both the number of foci and size of largest focus reported.

Background: The majority of cutaneous squamous cell carcinomas (SCCs) of the head and neck are low risk. However, a small subset will develop regional metastasis, and regional involvement of the parotid gland lymph nodes is a strong predictor of concurrent cervical lymph node involvement and aggressive disease. The current clinical staging of cutaneous SCC is limited, as only N1/N0 disease is reported, compared to mucosal SCC, where there are 5 categories (N1, N2a/b/c, N3).
Objective: In this study, the authors attempt to identify independent pathological variables to modify the current staging system for head and neck cutaneous SCC.
Participants/Methods: 215 patients with biopsy-proven cutaneous SCC of the head and neck who developed parotid area metastasis were evaluated. All patients had surgery as their primary treatment, and 175 also had adjuvant radiotherapy. Clinicopathologic features were recorded, including the number of foci of metastatic SCC, the presence of extracapsular spread (ECS), and the size of the largest focus of metastatic SCC. Univariate and multivariate analysis was performed to identify features that predicted survival. The proposed staging system was then applied to a different cohort of patients from another institution with cutaneous SCC metastatic to the parotid and followed for at least 2 years.
Results: The initial patient cohort of 215 patients had an overall 5-year survival of 69% and a 5-year locoregional control rate of 73%. Pathologic findings that significantly predicted survival included the number of metastatic SCC foci (single or multiple) in the parotid basin and size of the largest metastatic focus (≤3 cm or >3 cm). The presence of ECS was also an adverse predictor of survival, but was not an independent predictor on multivariate analysis. A proposed staging system (N1S3) for parotid area cutaneous SCC metastases was developed as follows: Stage I, single lymph node involved measuring ≤3 cm; Stage II, single lymph node >3 cm or multiple lymph nodes ≤3 cm; and stage III, multiple lymph nodes involved with at least 1 node >3 cm. When externally validated on a separate cohort of 250 patients, this system was a highly significant predictor of survival. Patients with N1S3 stage I disease had a 5-year overall survival of >90% compared to <70% for patients with N1S3 stage III disease.
Conclusions: Pathologists should report both the number of foci and the greatest size of tumor deposit in patients with cutaneous SCC metastases to the parotid region.
Reviewer's Comments: While not an independent predictor of survival in this paper, the presence of ECS remains an important finding to report for head and neck SCC. At our institution, the presence of ECS will prompt directed radiotherapy in addition to other required therapy. (Reviewer-Deborah J. Chute, MD).

Keywords: Metastatic Squamous Cell Carcinoma, Staging System, Extracapsular Spread

Print Tag: Refer to original journal article

Can We Do Better at FNA Diagnosis of Phyllodes Tumor?

Cytological Clues in the Distinction Between Phyllodes Tumor and Fibroadenoma.

El Hag IA, Aodah A, et al:

Cancer Cytopathol 2010; 118 (February 25): 33-40

FNA can be used with reasonable sensitivity to diagnose phyllodes tumors of the breast.

Background: Phyllodes tumors and fibroadenoma (FA) of the breast are fibroepithelial lesions characterized by a proliferation of both stromal and epithelial elements. The clinical management of these tumors is extremely different however, as phyllodes tumors have a high risk of recurrence and require radical excision with wide margins, while FAs are treated conservatively. Fine-needle aspiration (FNA) of the breast is notorious for a low sensitivity in the detection of phyllodes tumors.
Objective: To review the cytologic features of phyllodes tumors and FAs and to define an improved set of criteria for the detection of these lesions.
Methods: A 5-year review of breast lesions histologically diagnosed as phyllodes tumor or FA that underwent preoperative FNA were studied. Only those cases with adequate FNA material and surgical material available for review were included. Phyllodes tumors were classified as benign, borderline, or malignant using the World Health Organization criteria. FNA features of both phyllodes tumors and FAs were recorded, including cellularity of the smears, epithelial atypia, quantity and quality of stromal fragments, degree of discohesion, and dispersed cell atypia. Three features with the best sensitivity for phyllodes tumors were then presented to 2 independent cytopathologists, who then examined and categorized a mixed, blinded set of FA and phyllodes tumor FNAs.
Results: 15 cases of phyllodes tumor and 12 cases of FA were included. Eight phyllodes tumors were benign, 6 were borderline, and 1 was malignant. Of the 15 phyllodes tumors, only 6 (40%) were diagnosed preoperatively. There was no significant difference in cellularity or epithelial atypia between lesion types. Three features of the stromal and spindle cell fragments showed significant differences between phyllodes tumors and FAs. (1) There were significantly more discohesive spindle cells (with tapered nuclei rather than oval naked nuclei of myoepithelial cells) in the phyllodes tumor group. (2) Small fragments of cohesive fibroblastic cells forming a monolayer were seen exclusively in nearly all phyllodes tumors. (3) Finally, thin, tapered spindle cell nuclei (rather than plump and oval nuclei) present in a fragment of fibromyxoid stroma were seen exclusively in phyllodes tumors. Using these 3 criteria, the sensitivity of FNA for the diagnosis of phyllodes tumor was increased to nearly 100% on blinded review.
Conclusions: FNA biopsy can be used to differentiate phyllodes tumors and FA of the breast with a high sensitivity.
Reviewer's Comments: The diagnosis of malignant phyllodes tumor is relatively straightforward, even on FNA. Where FNA has classically failed is in the detection of benign and borderline phyllodes tumors. This study identifies 3 promising criteria that may be of use in classifying low-grade fibroepithelial lesions of the breast on FNA. (Reviewer-Deborah J. Chute, MD).

Keywords: Phyllodes, Fibroadenoma, FNA, Features, Differentiation

Print Tag: Refer to original journal article

Pituitary Tumor Transforming Gene and Adenoma Subtypes

Immunohistochemical Expression of Pituitary Tumor Transforming Gene (PTTG) in Pituitary Adenomas: A Correlative Study of Tumor Subtypes.

Salehi F, Kovacs K, et al:

Int J Surg Pathol 2010; 18 (February): 5-13

The PTTG protein product is differentially expressed among various pituitary adenoma subtypes.

Background: The pituitary tumor transforming gene (PTTG) produces a protein product that is involved in numerous cell processes ranging from angiogenesis to DNA repair. In addition to being expressed in a number of solid cancers, overexpression of PTTG has been demonstrated in pituitary adenomas. In mouse models, ablation of PTTG expression results in decreased tumor formation, while PTTG overexpression has the opposite effect. It is unclear if PTTG expression differs among various adenoma subtypes.
Objectives: To characterize the expression of PTTG in pituitary adenoma subtypes.
Methods: 89 surgically resected and routinely processed pituitary adenomas were randomly selected for analysis. Specimens included various tumor subtypes that had been previously subclassified using immunohistochemical (IHC) staining: growth hormone (12), prolactin (9), adrenocorticotropic hormone (ACTH) (10), follicle-stimulating hormone/luteinizing hormone/α (FSH/LH/α)-subunit (11), thyroid stimulating hormone (TSH) (9), null-cell (14), bromocriptine-treated prolactin (PRL) (13), and octreotide-treated growth hormone (GH) (11) tumors. Further IHC staining using a monoclonal antibody to PTTG (1:75) was then performed on each tumor case. PTTG staining was assessed at high magnification (x400) for both expression intensity (0=none; 1=mild; 2=moderate; 3=strong) and percent positivity (percent positive cells in each high-power field). A histological score for PTTG expression was then calculated by multiplying the expression intensity score by the percentage of positive cells. Statistical analyses were then performed.
Results: All positive cases showed cytoplasmic staining that was most prominent in the paranuclear region (Golgi zone). No nuclear PTTG staining was identified. The mean percentage of PTTG positive tumors among all tumor subtypes was 52%, with the highest percent positivity within GH tumors (94%) and the lowest percent positivity within the PRL adenomas (21%). The mean expression intensity of PTTG among all tumor subtypes was 1.62, with the highest intensity observed in GH tumors (2.40) and the lowest intensity observed in treated PRL tumors (0.36). The mean histological score for all PTTG-positive tumors was 110, with the highest score observed in null cell adenomas (200) and the lowest score observed in PRL adenomas (34). The histological score was significantly lower in treated versus untreated GH adenomas. There was both high intraobserver (0.93) and interobserver (0.87) agreement for PTTG interpretation.
Conclusions: PTTG is differentially expressed in subtypes of pituitary adenoma, and its expression in GH tumors is influenced by prior treatment with somatostatin analogue medications.
Reviewer's Comments: It would be interesting to know if PTTG expression differs among the various GH tumor subtypes, since the clinical behavior of "classic" GH tumors differs from the reportedly more aggressive sparsely granulated GH tumor subtypes. (Reviewer-T. David Bourne, MD).

Keywords: PTTG Immunostaining, Pituitary Adenoma

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Pediatric Renal Kidney Transplant Findings

Patterns of Chronic Injury in Pediatric Renal Allografts.

Dart AB, Schall A, et al:

Transplantation 2010; 89 (February 15): 334-340

Significant tubulointerstitial and vascular injury is seen in pediatric renal allografts by 5-year post-transplantation.

Background: While the findings and clinical determinants of chronic allograft injury are relatively well-defined in adults, the same is not true for pediatric renal allografts.
Objectives: To better define the natural history of chronic renal allograft injury in pediatric patients as reflected by changes within the tubulointerstitial, vascular, and glomerular compartments during the first 5 years after transplantation and to determine the underlying clinical determinants of these types of injuries.
Methods: 240 renal biopsy specimens from patients enrolled in the pediatric protocol biopsy program at the Children's Hospital of Winnipeg were included in the study. All patients had received immunosuppressive regimens prior to biopsy. Acute rejection (AR) was subclassified into the following 4 categories: clinical AR, subclinical AR, borderline AR, and persistent AR. Renal biopsies were performed for the following indications: protocol (1, 3, 6, and 12 months); evaluation of cause of acute renal allograft dysfunction; 1-month biopsies to document effects of immunosuppressive therapy. Biopsies were examined using light microscopy as well as immunofluorescence (IF) and electron microscopic analysis if there was a clinical concern for new or recurrent glomerular disease. IF for C4d and immunohistochemistry for SV-40 and/or in situ hybridization (BK viral probes) were performed for selected cases. The changes of chronic injury were scored on a scale from 0 to 3. Clinical determinants for allograft injury included donor and recipient variables, obesity, hypertension, human leukocyte antigen (HLA) compatibility, acute tubular necrosis, and calcineurin inhibitor (CNI) trough levels. Clinical evaluation of renal allograft function was performed using serum Cr measurements (each clinic visit), annual nuclear glomerular filtration rate (GFR) testing, and annual protein determinations (24-hour urine classification).
Results: The main patterns of chronic injury in pediatric renal allografts included interstitial fibrosis, tubular atrophy, vascular fibrous intimal thickening, arteriolar hyalinosis, glomerulopathy, and increased mesangial matrix expansion. Changes of chronic tubulointerstitial injury were most frequently identified during the first 12 months after transplant. In contrast, global glomerulosclerosis and vascular damage were more often seen >24 months after transplant. Determinants of chronic interstitial fibrosis included borderline rejection histology, acute rejection, and obesity, among others. Determinants of chronic tubular damage included AR and acute tubular necrosis, among others. Vascular damage was primarily associated with donor hypertension. Antibody induction therapy was associated with protection from the development of chronic interstitial fibrosis, tubular damage, and arteriolar hyalinosis.
Conclusions: Pediatric renal allografts show a significant number of chronic tubulointerstitial and vascular changes during the first 5 years after transplantation. These changes are associated with a number of clinical variables, including donor hypertension, obesity, acute tubular necrosis, rejection, and CNI toxicity, as expected.
Reviewer's Comments: The findings in this study are well-presented and relatively comprehensive for this age cohort. Pathologists should look carefully for early signs of CNI toxicity. (Reviewer-T. David Bourne, MD).

Keywords: Transplant Nephropathy, Pediatric

Print Tag: Refer to original journal article

Recurrent Micropapillary DCIS Independent of Nuclear Grade

Micropapillary Ductal Carcinoma In Situ of the Breast: An Inter-Institutional Study.

Castellano I, Marchiò C, et al:

Mod Pathol 2010; 23 (February): 260-269

Micropapillary DCIS is more likely to recur after breast-conserving surgery than conventional DCIS. High nuclear grade is associated with worse clinicopathologic features than those with low- or intermediate-grade nuclei.

Background: Widespread mammography screening is increasing the detection of ductal carcinoma in situ (DCIS), accounting for 20% of the breast carcinomas from a screened population. Breast conserving surgery is offered as an alternative to radical mastectomy, but the recurrence rates of DCIS with possible progression to invasive disease is still 10% to 15%. Predicting those with increased chance of recurrence may provide guidance for therapeutic choices, but the relevance of architectural patterns, especially micropapillary growth, is controversial.
Objective: To characterize micropapillary DCIS for prognostic significance.
Methods: 55 cases of micropapillary DCIS, defined as 95% of ducts having a micropapillary pattern, were collected and assessed for clinicopathologic features, particularly nuclear grade, extent, necrosis, microinvasion (<1 mm), ER/PR status, Ki67, HER2 amplification, EGFR, and p53.
Results: The indication for biopsy was calcifications in all cases, but 3 also had nipple discharge with positive cytology. Nuclear grade was stratified as 24% low-, 29% intermediate-, and 47% high-grade DCIS. The mean follow-up was 74.3 months. Of those with breast conserving surgery with or without radiation, recurrence occurred in 31%, most of which was invasive carcinoma. Radiation did not affect the recurrence rate, and only high nuclear grade had a significant correlation with recurrence. High nuclear grade was more likely to overexpress HER2, have higher mitotic activity, necrosis, microinvasion and more extensive disease than low or intermediate grade. The remaining 34% of the patients had mastectomy due to extent of disease. The micropapillary DCIS was more likely to recur, independent of nuclear grade, than a comparable non-micropapillary DCIS cohort (P =0.019).
Conclusions: Micropapillary DCIS with high nuclear grade is associated with more aggressive clinicopathologic features and risk of recurrence compared to low or intermediate nuclear grade. But, the micropapillary architecture alone confers a greater risk of local recurrence after breast-conserving surgery when compared to conventional (non-micropapillary) DCIS.
Reviewer's Comments: DCIS with the micropapillary architecture is important to note, as it alone confers a greater risk of recurrence after breast-conserving surgery. Radiation did not appear to decrease this recurrence. However, nuclear grade is also associated with more aggressive clinicopathologic features and should be noted accordingly. (Reviewer-Mary T. Galgano, MD).

Keywords: DCIS, Micropapillary Type

Print Tag: Refer to original journal article

Subclassifying BI-RADS 4 Microcalcifications

Clinical Implications of Subcategorizing BI-RADS 4 Breast Lesions Associated With Microcalcification: A Radiology–Pathology Correlation Study.

Sanders MA, Roland L, Sahoo S:

Breast J 2009; 16 (January/February): 28-31

The optional subclassification of microcalcifications in the BI-RADS category 4 lesions stratifies the risk of malignancy.

Background: The Breast Imaging Reporting and Data System (BI-RADS) for grading the level of concern for malignancy in a screening mammogram serves to standardize radiographic interpretation. This standardization begins the process of risk stratification for appropriate patient evaluation and safety. It allows for easier correlation of radiographic impression and pathologic diagnosis to determine necessary call backs for re-biopsy. The BI-RADS categories describe probabilities of malignancy, for example, category 3 is associated with <2% chance of malignancy, but category 4 is associated with 23% to 30% malignancy. Category 5 is considered highly suggestive of malignancy, with about 95% diagnosed as such on biopsy.
Objective: To evaluate the significance of subclassifying BI-RADS 4 based on the type of microcalcifications to further stratify the risk of malignancy on biopsy.
Methods: A retrospective review of breast needle core biopsies (NCB) performed for microcalcifications in the absence of a mass lesion was performed. BI-RADS categories and subcategories of 4 that had been routinely assigned were documented. Cases with multiple diagnoses were reviewed to determine which lesion was associated with the noted microcalcifications.
Results: Of 239 consecutive NCBs, 74% were benign, 3% were atypical epithelial hyperplasia, and 23% were malignant (predominantly ductal carcinoma in situ). All 239 biopsies were BI-RADS 4, but only 191 were subclassified. These were distributed as 49% 4A (low suspicion for malignancy), 38% 4B (intermediate suspicion for malignancy), and 13% 4C (moderate concern, but not classic for malignancy). Of the BI-RAD 4C, 70% were associated with malignancy compared to only 21% of 4B and 10% of 4A. This does not include incidental lesions (not associated with the targeted microcalcifications), including 4 cases of lobular carcinoma in situ.
Conclusions: Subclassification of the BI-RADS category 4 lesions based on microcalcifications not associated with a mass lesion has implications for risk of malignancy and may be helpful for correlating pathology results to the radiographic impression.
Reviewer's Comments: Most of the biopsies we see are BI-RADS 4, and these authors show that 4C lesions are more similar to BI-RADS 5 than they are to 4A/B lesions. Negative biopsy results of a 4C lesion should prompt a more careful correlation to assure the appropriate microcalcifications were sampled. (Reviewer-Mary T. Galgano, MD).

Keywords: Breast Cancer Screening, BI-RADS

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Morphological Features of CA in Patients With SSAs

Identification of Histologically Distinct Conventional Adenomas That Arise Predominately in Patients With Sessile Serrated Adenomas.

Pai RK, Mackinnon AC, et al:

Am J Surg Pathol 2010; 34 (March): 355-363

Tubular adenomas that develop in patients with sessile serrated adenomas have unique features.

Background: Sessile serrated adenomas (SSAs) are precursor lesions for many sporadic microsatellite instability high (MSI-H) colonic adenocarcinomas. Within this pathway are also included traditional serrated adenomas, that is to say, polyps with dysplastic epithelium and serration. These lesions have been shown to be associated with *BRAF* mutation and frequent CpG methylation of gene promoters. Cancers that arise through this pathway account for 10% to 20% of colorectal adenocarcinomas. It has been shown that patients without a known genetic predisposition for colon cancer, who develop SSAs, are at increased risk for having other polyps of this pathway and also have increased risk for otherwise conventional-appearing adenomas.
Objective: This study investigated the morphologic features of apparently conventional adenomas (CAs) in patients with SSAs.
Methods: An institution's surgical pathology database was searched for all SSAs. Additional polyps from these patients were reviewed and classified. One hundred CAs from 70 of these patients were reviewed and compared to 79 control CAs from 37 patients. The following features were recorded: cytoplasmic eosinophilia; focal serration; crypt dilatation; villousity; luminal debris; crypt branching; dystrophic goblet cells; and intraepithelial lymphocytes. *BRAF* and *KRAS* mutational analysis, as well as CpG island methylation status, were performed on select cases. Immunohistochemistry was performed with antibodies to MUC6.
Results: There was no difference in the sex and age of the patients or the site of the polyps between the study and control groups. Study polyps were larger on average by 1.6 mm. Study polyps were more likely to show striking cytoplasmic eosinophilia, focal serration, and crypt dilatation. Polyps with these features were then considered to be atypical. Atypical adenomas tended to be more likely to be located in the right colon. Interestingly, *BRAF* and *KRAS* mutations were not identified in any polyps tested. Atypical adenomas were more likely to show CpG-island methylation compared to typical adenomas. They were also more likely to express MUC6.
Conclusions: Some otherwise conventional-appearing colonic adenomas appear to develop within the SSA pathway, and histologic features as well as MUC6 immunohistochemistry are helpful for predicting this. Patients who have SSAs are more likely to develop these lesions. The authors suggest that this may correlate with an overall genetic "field effect" within the colon.
Reviewer's Comments: This study reflects our increased knowledge regarding the development of some colon cancers and further highlights the difficulty distinguishing the various polyps that develop within the colon. (Reviewer-Edward B. Stelow, MD).

Keywords: Sessile Serrated Adenomas, Tubular Adenomas, MUC6, Histology

Print Tag: Refer to original journal article

Prostate Cancer Diagnosis May Increase Suicide Risk

Immediate Risk of Suicide and Cardiovascular Death After a Prostate Cancer Diagnosis: Cohort Study in the United States.

Fang F, Keating NL, et al:

J Natl Cancer Inst 2010; 102 (March 3): 307-314

The diagnosis of prostate cancer may increase the immediate risk for suicide.

Background: After the advent of prostate-specific antigen (PSA) testing, prostate cancer has come to be one of the most common malignancies diagnosed. The prognosis is highly variable, and some patients diagnosed with prostate cancer can live for extended periods of time, even without any therapeutic intervention. Recently, it has been noted that the diagnosis itself is dangerous, and newly diagnosed patients may be at increased risk for suicide or cardiovascular death.
Objective: To investigate the risk for these stress-related causes of death in U.S. men newly diagnosed with prostate cancer.
Methods: Surveillance, Epidemiology, and End Results (SEER) data were used to identify patients with primary prostate cancer diagnoses and their outcomes. These data were linked to data from the National Death Index containing both time and cause of death. Risks for suicide and cardiovascular death were calculated for the year following the diagnosis of prostate cancer. These numbers were compared to risks of death from these causes in men from the general population.
Results: Nearly 350,000 patients diagnosed with prostate cancer were included in this study, and the average age at diagnosis was 70.2 years. Most patients were married and white. One hundred forty-eight men with cancer committed suicide compared to the 108 expected (risk = 1.4). The risk was greatest in the first 3 months after diagnosis. Interestingly, the risk has decreased since the use of widespread PSA testing. Being single or having metastatic disease was associated with increased risk of suicide. There was a slight increase in the risk of cardiovascular death (risk = 1.09). This peaked during the first month after diagnosis. This risk remained similar after the widespread use of PSA testing.
Conclusions: The authors speculate that a diagnosis of prostate cancer may increase the immediate risk of suicide and cardiovascular death.
Reviewer's Comments: It is most interesting that the risk of suicide after the diagnosis of prostate cancer has decreased with the use of widespread PSA testing. This suggests that increased rate of diagnosis may have led to better understanding and less fear of the disease. (Reviewer-Edward B. Stelow, MD).

Keywords: Prostate Cancer, Suicide, Diagnosis, Heart Attack

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