promoter hypermethylation is not uncommon in melanomas. The functional interaction between activated MEK/ERK signaling and loss of p16 in melanoma development is largely unknown.
Design: Specimens of melanoma (n=10), metastatic melanoma (n=10), dysplastic nevi (n=10), compound nevi (n=10) and Spitz nevi (n=10) were retrieved, and sections stained immunohistochemically to detect MEK/ERK activation (phospho-MEK) and p16 expression. Markers of cell proliferation (Ki-67) and anti-apoptosis (BCL2) were examined for correlation with status of MEK/ERK and p16 expression. The level of positivity was scored by the percentage of stained melanocytic cells (0-100%) times the staining intensity (1-3) and was statistically analyzed.
Results: Phospho-MEK expression is highest in primary melanomas (score: 77) and dysplastic nevi (score: 68), whereas metastatic melanomas have much lower staining activity (score: 27). Spitz and compound nevi have low levels of phospho-MEK expression (score: 3 and 11, respectively). Compound, dysplastic, and Spitz nevi are diffusely positive for p16, with average scores of 240, 222, and 216, respectively and exhibit both nuclear and cytoplasmic staining in > 50% positive cells. The expression of p16 decreases in primary melanomas (score:155), and has lowest level in metastatic melanomas (score: 30). Colocalization of phospho-MEK and p16 is present in < 15% positive cells in melanoma and dysplastic nevi. Interestingly, we found that levels of BCL2 closely correlate with p16: the expression of BCL2 follows the same trends of p16 in the compound and dysplastic nevi which were expressed strongly to moderately, positive in 89% cells and had an intensity of 2.6 (score: 231). The proliferation index with Ki-67 is slightly higher in melanomas (8-10%) than nevi (0-5%).
Conclusions: Low levels of phospho-MEK in nevi indicate that NRAS and BRAF mutations are not sufficient to induce MEK/ERK signaling activation. Co-existence of phospho-MEK and loss of p16 in melanomas suggest their functional interaction in maintaining the malignant phenotypes of these cells. The correlation between p16 and BCL2 needs to be further explored for functional significance. (* These authors contribute equally to this project).

Education

475 Pathology Education as a Web Application: An Advanced Tool for the Future Pathologist

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Background: As part of the Integrated Medical Information Technologies System (IMITS) Telepathology Project, a reference database of pathology cases was developed to further pathology education in the highly distributed Air Force medical environment. Customized software displays digital slide pathology images in context, both with realistic background information and added notes and annotations from an experienced pathologist. The instructor can set up tests that send the student directly to an area of interest on an image, display essay and multiple choice questions, and save the answers for later grading. The graded results are immediately available through the system for the student's review.
Design: A database in MS SQL Server was developed and loaded with cases containing anonimized clinical history, histologic, and diagnostic information. Slides from those cases were scanned on various commercial Whole Slide Imagers: Aperio's ScanScope, Zeiss's Mirax (Trestle DSM), and Hamamatzu's Nanozoomer. The images were stored on a SAN and the urls loaded into the database. The web application, written in MS C# language using .NET framework 2.0, invokes an appropriate viewer when an image is selected. Demonstration of the system will focus on oral and dermatological pathology, as the principal investigators for the Air Force and UPMC respectively practice those specialties.
Results: The centralized server allows student users and instructors to access the repository at their convenience, using readily available web browsers to review images in context of the case diagnostic information. Both the student and the instructor have the ability to operate asynchronously, accessing the system without concern for interrupting critical tasks. Background procedures collect statistics transparently for feedback to improve the system.
Conclusions: Users at all levels will benefit from access to digital slide images organized in a repository categorized by type of tissue and disease. Student users can benefit even more by taking the tests, and then seeing feedback on their diagnoses from an experienced pathologist.

476 The Use of Multimedia Files, Podcasts, and Webcasts in Pathology Education

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Background: Multimedia files (MMF) including video and sound have been used in pathology resident education (PRE) but have required considerable investments in hardware and software and specialized technical support.The widespread use of hand held devices such as cell phones and PDAs have stimulated the expansion of technologies for the development of portable MMF that can be distributed with inexpensive software. The use of Podcasts (PC) for educational activities in PRE has not been previously reported.
Design: Ten MMF including videos recording the examination of a pathology slide under light microscope and audio descriptions were prepared using a digital camera, readily available presentation software (PowerPoint, Microsoft, Redmond, WA), and low cost software (Quicktime Pro, Apple, Cupertino, CA).The MMF were developed in "pairs": video quizzes (VQ) and corresponding teaching files providing "answers", descriptions and diagnostic pearls. The size of the VQ was maintained to allow for file transfer by e-mail via free SMTP systems (Simple Mail Transfer Protocol, <15 MB) or posting for webcasting (WC) and PC. Files were converted into .AVI and .MOV formatting for viewing with open source multimedia framework viewers and .M4V formatting for PC. A PC was formed by joining a free PC/WC host service (SwitchPod, Wizzard Media, Pittsburgh, PA). Files were transmitted to all residents and faculty. MMF were viewed using laboratory desktop computers and cell phones (Iphone, Apple, Cupertino, CA). A 5 point scale survey (1 =lowest score to 5=highest) was transmitted with each VQ to assess satisfaction with the platform. Compliance rates and diagnostic accuracies were recorded.
Results: There were 55 e-mail responses for the VQs, and 89 downloads from the podcast viewing platform over a period of one month. Twenty percent responded to the unsolicited VQs, and 100% of those that responded participated >=2 occasions. Results of the VQs showed approximately 80% correct answers for both residents and faculty. Satisfaction scores were: Image quality – 4.4 (range 2-5); Sound quality-4 (range – 0-5); Ease of use – 4.7 (range 3-5); Satisfaction with format- 4.7 (range 3-5). Negative comments were mostly related to suboptimal sound transmission (14.5%).
Conclusions: MMF including images and sound that can be transmitted via e-mail or posted for PC or WC, are a useful tool for PRE. The MMF can be viewed from personal computers, selected cell phones, or other portable devices that allow internet access. The use of this methodology in PRE is discussed.

477 Gross Examination and Patient Safety (GEPS) Residents' Teaching Conference

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Background: We recently established a monthly conference in our department for residents' education: the Gross Examination and Patient Safety (GEPS) Conference. The coordinator is an attending pathologist, with participation by the residency program director and the director of anatomic pathology. Attendance is mandatory for all pathology residents. Cases with problems that occurred in the gross room are flagged by the faculty, pathologist assistants, transcriptionists, histotechnologists, and/or residents. Each case is then presented in an anonymous fashion, with the format consisting of glass slides, gross photos, and/or copy of the gross description. Pertinent references are discussed including sections from manuals of gross examination, textbooks of surgical pathology, CAP checklists for inspection and accreditation, and literature on quality assurance, patient safety and medico-legal aspects of pathology. The goal of this teaching conference is process and performance improvement to help ensure patient safety.
Design: We reviewed the cases presented at the conference over the past 4 months and classified problems in gross examination and reporting. We analyzed individual and system errors and described the corrective actions implemented.
Results: There were 55 cases presented, categorized into 9 different types of problems including incomplete/inadequate gross examination (10 cases); incomplete/inadequate gross description (12 cases); improper labeling/identification (5 cases); too few sections submitted for histologic examination (3 cases); too many sections submitted (1 case); delay in processing (6 cases); inadequate triage of tissue (3 cases); sections inadequate for optimal histologic processing (13 cases) and other issues (2 cases). Examples of system errors identified include suboptimal work flow of specimens in the gross room, lengthy and redundant gross descriptions due to templates that needed revision, and delay in specimen processing due to lack of priorization for grossing specimens.
Conclusions: We report our novel monthly residents GEPS conference. We propose it as a constructive, non-threatening educational conference for process improvement that especially addresses problem-prone situations. We believe this type of conference provides a unique opportunity to help residents identify common and uncommon individual and system errors in order to insure higher quality pathologic gross examination and thereby improve medical care and patient safety.

478 An Interactive Web-Based Teaching Tool for Hematopathology

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Background: Although numerous online resources of medical knowledge are available, considerable variability exists in terms of depth and quality of content, website design, and features that are relevant to medical practice. We present a novel interactive teaching and reference hematopathology tool for pathologists and clinicians.
Design: This interactive atlas and text of hematopathology was built on a relational database designed to handle structured medical knowledge. The description of each entity is parsed into units: Key Features, Epidemiology, Clinical, Histopathology, Immunophenotype, Genetics, Prognosis, etc. A bi-directional interface provides a seamless connection from this knowledge base to PubMed. An author interface was designed to allow direct entry of text, images, and metadata into the database. A permission system was installed to manage the work flow of authoring, editing, and publishing. Server software was implemented to automatically create an additional customized version for hand held devices and cell phones.
Results: This electronic atlas of hematopathology can be viewed on any internet connected computer or wireless device. The content includes highly organized text, high resolution image thumbnails that can be enlarged, a search engine that allows searches based on any combination of clinical, pathologic or image criteria, and references that are directly linked to PubMed abstracts. In addition, the system develops links to up-to-date PubMed references for each subheading of the disease entity. A differential diagnosis (DDx) link displays side by side comparisons of images and Key Features for relevant lesions, and end users can rapidly create their own customized DDx tables. On preliminary demonstration surveys, this tool was well received by pathology and oncology trainees as well as practitioners.
Conclusions: This system provides an electronic book that is visually rich, offers dynamic pages, is easily customizable, and provides realtime access to literature updates. For the authors, it provides an intuitive authoring tool for updating the content. The hand held device/cell phone version provides access to knowledge in the clinics and at the bedside. As a possible future application, the architecture of the database allows

presentation of this information within electronic medical records. Thus, any provider reviewing a patient record will have immediate access to detailed and current knowledge on that patient's particular leukemia or lymphoma.

479 Virtual Educational Portal for the Digital Slide Image Repository at a Large Academic Multi-Institutional Center

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Background: At the University of Pittsburgh Medical Center, because of geographic logistics, the educational use of glass slides has been difficult. Capturing glass slides digitally became the solution to providing availability. The premise is for educational slides to be viewable at any computer and at any institution associated with UPMC. In order to unite the entire collection of educational digital slides from the different sites and servers, we developed a web-based "virtual" portal which provides the main gateway by which our entire digital slide image repository can be easily accessed and utilized by even the most amateur of users.

Design: The educational teaching slides are scanned and captured on the Trestle Digital Slide Maker (DSM) or Aperio ScanScope system and stored on a Stored Area Network (SAN) server. Digital viewers include the proprietary ImageScope and Trestle's Java viewer. The database used to provide context is Microsoft SQL Server. The web based portal is created on a SUNONE platform via a Cold Fusion MX Enterprise Middleware.

Results: Since early 2004, over 5000 digital slide images have been scanned and collected, with our web based portal only recently providing centralized access. Medical students, residents, fellows, or attendings no longer need to go to specific physical locations to obtain glass slides. Training is facilitated with the web-based viewers. When using the Trestle viewer, history and case notes can be annotated on the slide simulating a question and answer format. Key histologic features can be marked aiding in training an inexperienced eye. Distribution of unknown slides is performed without the need for multiple recuts, loss of material, or transportation hindrances.

Conclusions: With our digital slide images, the entire slide is captured digitally and therefore simulates the reality of evaluating a glass slide. Skills such as screening, finding the essential areas of interest, and knowing how to navigate through a slide can be practiced over the internet. With static images, because the area of interests are immediately shown, these key intangible skills are lost in the learning process. Our centralized web portal provides an invaluable tool and further enhances our commitment to education in pathology.

Endocrine

480 A Comprehensive Survey of Kinase Pathway Mutations in Poorly Differentiated Thyroid Carcinomas Using High-Throughput Mass Spectrometry-Based Genotyping

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Background: Poorly differentiated thyroid carcinoma (PDTC) represents the major cause of death from thyroid carcinomas. Aim: 1) To perform a comprehensive screen for known thyroid cancer-associated kinase pathway mutations in PDTC using a high throughput genotyping technique. 2) To correlate the mutation status with known clinicopathologic parameters.

Design: PDTC were defined on the basis of high mitotic activity and/or tumor necrosis. DNA was extracted from 43 paraffin-embedded tissue blocks from 36 patients. The samples were then genotyped using a highly multiplexed Sequenom mass spectrometry-based mutation assay that screened for 11 mutations in *BRAF,* 8 in *NRAS,* 7 in *HRAS* and 11 in *PIK3CA*. Mutations were confirmed by direct sequencing.

Results: Overall, mutations were found in 14 (39%) of the 36 samples tested. *BRAF* V600E mutations were identifed in 7 (19.4%) of 36 patients with the following phenotypes (3 tall cell, 2 non-tall cell papillary, 1 follicular, 1 with a mixture of follicular, oncocytic and papillary). *NRAS* mutations at codon 61 were found in 6 (17%) of the 36 cases (including 3 non-tall cell papillary, 2 follicular, 1 with a mixture follicular, oncocytic and papillary). Only 1 patient had *HRAS* mutation at codon 61, in a PDTC with a follicular phenotype. Mutation at codon 1047 of *PIK3CA* was detected in one tumor with a papillary phenotype. One patient had concomitant *BRAF* V600E and *NRAS* mutations, both confirmed by direct sequencing; this tumor showed a mixture of Hurthle, follicular and nuclear papillary areas. *BRAF* mutation was present in all PDTC with tall cell morphology (3 of 3, 100%) and in only 4 (12%) of the 33 remaining patients (p=0.005). The mortality rate from PDTC was 67%. There was no significant correlation between the mutation status and other clinicopathologic parameters such as extra-thyroid extension (ETE) and survival. The presence of ETE and extra-thyroid vascular invasion correlated with death of disease (p=0.004, 0.017 respectively).

Conclusions: 1) Kinase pathway mutations are present in a substantial number (39%) of patients with PDTC.2) Although extra-thyroid extension rather than mutation was a predictor of outcome, a significant number of PDTC may be amenable to targeted therapy based on the presence of certain kinase pathway mutations.

481 Thyroid Pathology in PTEN Hamartoma Tumor Syndrome (PHTS): A Clinocopathologic and Molecular Genetic Analysis of a Distinctive Entity

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Background: PHTS is a complex disorder caused by germline inactivating mutations of the PTEN tumor suppressor gene. Carriers develop both benign and malignant tumors in a variety of tissues, including thyroid in two-thirds. The purpose of this study is to investigate whether there is correlation between the thyroid pathology and the PTEN mutation in a specific exon.

Design: All thyroid lesions from patients with known PTEN mutation were retrieved from the Departments of Pathology of Brigham and Women's Hospital and Children's Hospital. Specimen photographs, histopathology, clinical and molecular findings were reviewed.

Results: Eleven cases of PHTS [Cowden syndrome (CS) 7 cases; Bannayan-Riley-Ruvalcaba syndrome (BRRS) 4 cases] in 7 females and 4 males were studied. The mean age at diagnosis of the thyroid lesion was 27 years (range 11-68). Each thyroid had multiple pathologic findings including: multiple adenomatous nodules (MAN, n=7 cases), with focal clear cell changes (n=3 cases), papillary carcinoma (PTC, n=4 cases), follicular carcinoma (FC, n=3 cases), and multiple follicular adenomas (FA, n=2 cases). Eight cases (73%) showed marked lymphocytic thyroiditis, and one also had C cell hyperplasia. Correlation of the 7 germline mutations and pathologic findings revealed: exon 5 (cases 1, 2, 8) FC and MAN, multifocal PTC and nodular hyperplasia, and MAN, respectively; exon 6 (cases 5, 10, 11) PTC, multiple FAs and PTC microcarcinoma, and FC, respectively. The case with mutation in exon 8 (case 7) revealed FC and MAN.

Conclusions: Both benign and malignant multicentric and distinct thyroid lesions were observed in PHTS; no morphologic differences were seen between those in CS and BRRS. Although, there was no correlation between specific germline mutations (exons) and morphologic findings, the presence of MAN in a background of lymphocytic thyroiditis is distinct and characteristic of this syndrome.

Gender	Diagnosis	Age Diagnosis (yrs)	PTEN gene mutation	Thyroid Diagnosis
M	BRSS	24	R130Q; 389 G>a at codon 130, Exon 5	FC, MAN, LT
F	CS	38	Y180X, Exon 5	PTC, NH, LT
F	CS	34	No	MAN, PTCmicro, LT
F	CS	64	NA	MAN
F	CS	22	c.609_611delTCCinsATAAAT, Exon 6	PTC,MAN, LT
F	CS	48	NA	PTC, MAN
M	CS	12	c.968dupA, Exon 8	FC, MAN, LT
M	BRRS	23	c.389G>A, Exon 5	MAN, LT
F	CS	68	NA	PTC, FAs
F	BRRS	11	c.512-513InsA, Exon 6	FAs, PTCmicro
M	BRRS	13	c499_505del7ACTATTC, Exon 6	FC, LT

482 Familial Non-Medullary Thyroid Carcinoma: Morphologic Patterns Indicating an Inherited Trait

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Background: Non-medullary thyroid carcinoma (NMTC) is quite common, although only 5% are familial (FNMTC). Clinically, FNMTC can be divided into two major groups, syndromes characterized primarily by non-thyroid tumors [PTEN Hamartoma Tumor Syndrome (PHTS) and Familial Adenomatous Polyposis (FAP)] and those characterized primarily by FNMTC (FPTC).

Design: Thyroid cases of FNMTC were retrieved from our files, 1999 to 2007. Specimen photographs, stained slides, medical records, and molecular findings were reviewed. We correlated thyroid pathology with molecular genetic findings.

Results: We identified 22 cases of FNMTC (11 PHTS, 8 FAP, 3 Multiple FNMTC). PHTS (7 females and 4 males) had mean age of detection of a thyroid lesion at 27 years (range 11-68). The most common findings were multiple adenomatous nodules (MAN, 7 cases) with clear cell changes (3 cases), followed by papillary carcinoma (PTC, 4 cases), follicular carcinoma (FC, 3 cases), multiple follicular adenomas (FA, 2 cases), and C cell hyperplasia (1 case). Eight cases (73%) showed lymphocytic thyroiditis. Seven patients had confirmed PTEN germline mutations. Eight FAP patients (all females), had a mean age at diagnosis of thyroid carcinoma of 34 years (range 18-53). Five were diagnosed as PTC, cribriform-morular variant (CM-PTC), 2 as PTC, follicular variant, and one was classical PTC. Mean tumor size was 1.3 cm; seven cases were multifocal with multiple encapsulated nodules with marked sclerosis. In CM-PTC, the cribriform pattern predominated over the morular component, with no lymphocytic thyroiditis. Six patients had APC germline mutations. From the preponderance of FNMTC (FPTC) cases, one of three (mean age 56 years) with multifocal PTC had an abnormal tumor karyotype with a breakpoint in 19p13.2 suggestive a TCO gene mutation. Tumor size ranged from 0.8 to 2.5 cm. Two tumors were multifocal with extrathyroidal extension, vascular invasion and lymph node metastasis. Lymphocytic thyroiditis was uniformly present. Follow up (24 to 186 months) showed no tumor recurrence.

Conclusions: Multifocal involvement of the thyroid was a common feature in all FNMTC inherited tumor syndromes. Lymphocytic thyroiditis was present in both PHTS and multicentric FPTC. Characteristic morphologic findings, such as CM-PTC, MAN, and multicentric FPTC, should alert pathologists to notify clinicians of the possibility of an inherited trait, such as FAP, PHTS, or FPTC.

483 Immunohistochemical Expression of Notch Molecules in Human Pituitary Adenomas: Their Relationship with Subtypes of Adenomas

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Background: Notch signaling molecules (ligands and receptors) are type I transmembranous proteins that regulate the cell differentiation and proliferation through cell-cell interactions. Under the activation by Notch ligands, the Notch intracellular domain (NICD) is cleaved and translocated into the nucleus. So far, in human pituitary gland, it has been reported that *NOTCH3* mRNA was expressed in clinically non-functioning adenomas. NIH array database indicated that, in human pituitary gland, four Notch receptors (NTCH1, 2, 3, 4) and five Notch ligands (DLL1, 3, 4, Jagged1, 2) are identified. This study is aimed at to elucidate the relationship between the expressions