ANNUAL RESEARCH DAY PROGRAM  
DEPARTMENT OF PATHOLOGY AND LABORATORY  
MEDICINE  
UNIVERSITY OF OTTAWA  

Wednesday, April 14th, 2010  

AMPHITHEATER A- ROOM 2005  
ROGER GUINDON HALL  
HEALTH SCIENCES BUILDING  

8:55  WELCOME  

9:00-9:15  INTRACRANIAL MASQUERADE  
H. Faraji, John Woulfe, MD  
Department of Pathology and Laboratory Medicine, Ottawa Hospital, University of Ottawa  

9:15-9:30  INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM ARISING IN CYSTIC DYSTROPHY OF HETEROTOPIC PANCREAS  
M. Marinescu MD, Bich N. Nguyen MD FRCPC.  
Department of Pathology and Laboratory Medicine, Ottawa Hospital, University of Ottawa  

9:30-9:45  BREAST CANCER PROTEIN EXPRESSION AS A PROGNOSTIC MARKER IN SPORADIC EPITHELIAL OVARIAN CANCER (EOC): AN NCIC CTG OV.16 CORRELATIVE STUDY.  
J. I. Weberpals, D. Tu, J. Squire, S. Islam, MS. Amin, L. Pelletier, A. O'Brien, P. Hoskins, E. A. Eisenhauer; The Ottawa Hospital, Ottawa, ON; NCIC Clinical Trials Group, Kingston, ON; University of Ottawa, Ottawa, ON; BC Cancer Agency, Vancouver, BC  

9:45-10:00  SUDDEN DEATH IN SPLENIC ARTERY SEGMENTAL MEDIOLYTIC ARTERIOPATHY  
A. Edgecombe1, I. Teo1, M. Marinescu1 & C Milroy1,2  
1University of Ottawa, Department of Pathology & Lab Medicine, Ottawa, ON  
2Eastern Ontario Regional Forensic Pathology Unit, The Ottawa Hospital, Ottawa, ON
10:00-10:15  TWO BROTHERS WITH LIPOID PROTEINOSIS TEMPORAL CLINICOPATHOLOGIC CORRELATIONS WITH HISTOPATHOLOGICAL AND ELECTRON MICROSCOPIC FINDINGS
J.S. Manusow¹,², S. Brownstein¹,², A. Samad³, W.B. Jackson¹. ¹Department of Ophthalmology and ²Department of Pathology, University of Ottawa, Ottawa, Ontario. ³Department of Ophthalmology, Dalhousie University, Halifax, Nova Scotia.

10:15-10:45  BREAK AND POSTER VIEWING (ATRIUM)

10:45-11:00  INTRACYSTIC ONCOCYTIC PAPILLARY RENAL NEOPLASMS: A VARIANT OF EPITHELIAL PAPILLARY NEOPLASMS DISTINCT FROM PAPILLARY RENAL CELL CARCINOMA.
H. Faraji, K.T. Mai. Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

11:00-11:15  STUDY OF ENDOCERVICAL CURETTAGE SURGICAL PATHOLOGY SPECIMENS IN COLPOSCOPIC EXAMINATION
Farshid Siadat, Dr. Shahidul Islam
Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

11:15-11:30  UTERINE MULLERIAN ADENOSARCOMA WITH CHONDROSARCOMATOUS OVERGROWTH: A CASE REPORT
A. Edgecombe and M. Kyrollos
Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, ON

11:30-11:45  OCCULT CARDIAC AMYLOIDOSIS: A RARE CONTRIBUTOR OF POSTOPERATIVE DEMISE FOLLOWING CARDIAC SURGERY
T.A. Flood and J.P. Veinot. ¹Anatomical Pathology, The Ottawa Hospital, Ottawa, Ontario, Canada.
11:45-12:00 EXPRESSION PROFILE OF P16 (INK 4A) AND MIB1 (KI-67) IN HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) AND IMMATURE SQUAMOUS METAPLASIA (ISM) OF THE UTERINE CERVIX

**MS Amin**, PhD candidate; Mary Senterman, MD, FRCSC, FRCPC and Shahidul Islam, MD, PhD, FCAP

Division of Anatomical Pathology, The Ottawa Hospital, Eastern Ontario Regional Laboratory Association (EORLA), The Department of Pathology and Laboratory Medicine, The University of Ottawa, Ontario, Canada.

12:00-1:15 LUNCH AND POSTER VIEWING

(ATRIUM 2ND FLOOR, FACULTY OF MEDICINE)

1:15-2:15 GUEST SPEAKER

**DR. WENXIN ZHENG**

UNIVERSITY OF ARIZONA, COLLEGE OF MEDICINE

TITLE: ENDOMETRIAL PRECANCER AND CARCINOGENESIS

2:15-2:30 DIRECT mecA PCR TESTING FROM BLOOD CULTURE BOTTLES WITH GRAM POSITIVE COCCI IN CLUSTERS AND RETROSPECTIVE ANALYSIS OF ANTIBIOTIC USE

**Bing Wang**, Peter Jessamine, Karam Ramotar, Marc Desjardins, Angela Bonneau, Baldwin Toye

Division of Microbiology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital

2:30-2:45 CYTOLOGICAL FEATURES OF THYROID LESIONS DIAGNOSED AS INDETERMINATE FOR NEOPLASIA, WHICH PREDICT FOLLICULAR NEOPLASM ON FINE NEEDLE ASPIRATION ON BIOPSY OF THYROID (FNAB): A 5 YEAR RETROSPECTIVE STUDY IN OTTAWA HOSPITAL

**T Jayasinghe**, IT Ahmed, KT Mai, S Islam, NR Delatour, Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

2:45-3:15 BREAK AND POSTER VIEWING

(ATRIUM)
3:15-3:30 LUPUS NEPHRITIS: CLASSIFICATION REVIEW
WITH CLINICOPATHOLOGIC CORRELATION IN
PREDICTING RENAL OUTCOME
H. Faraji MD, Akram Elkeilani MD, FRCPC, Susan
Roberston MD, FRCPC

3:30-3:45 ANNOUNCEMENT OF PRIZE WINNERS AND
CONCLUSION

• Nadia Mikhael Award for Best Paper presented by a
  Junior Resident
• 2nd Best paper by a Junior Resident
• Virbala Acharya Award for Best Presentation by a
  Senior Resident or Fellow
• 2nd Best paper by a Senior Resident or Fellow
• Best Poster Presentation by a Graduate Student
• 2nd Best Poster Presentation by a Graduate Student
• Best Poster Presentation by a Resident
• 2nd Best Poster Presentation by a Resident
• Dr. M. Orizaga Award for Best Teacher
POSTERS

1- REGULATION OF APOBEC3G MEDIATED INTRINSIC IMMUNITY TO HIV INFECTION
Kasandra Bélanger, Halil Aydin, Olga Agah and Marc-André Langlois Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa.

2- SMALL MOLECULE ENHANCERS AND SKELETAL MYOGENESIS
Chenchen Hou1 and Qiao Li2 1-Honours Biomedical Sciences Program, Faculty of Science, University of Ottawa 2-Dept. of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa

3- RETINOID X RECEPTORS PLAY A KEY ROLE IN SKELETAL MUSCLE DEVELOPMENT
Melanie Le May, Qiao Li Departments of Pathology and Laboratory Medicine, and of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa.

4- NOVEL MULTIVALENT HIV PEPTIDES AND LIPOPEPTIDES INDUCE A STRONG CELL MEDIATED IMMUNE RESPONSE IN MICE.
Haitham T. Ghunaim, Francisco Diaz-Mitoma, Jose Torres, Ashok Kumar, David E. Anderson, and Ali Azizi.

5- ROLE OF THE 26S PROTEASOME IN THE ACTIVATION OF RETINOIC ACID RESPONSIVE GENES
Aliaa Higazi, Mahmoud Abedl, Jihong Chen and Qiao Li Departments of Pathology and Laboratory Medicine and of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

6- ROLE OF HISTONE ACETYLTRANSFERASE ACTIVITY IN THE SPECIFICATION OF CARDIMYOCYTE LINEAGE
Mach H, Lacroix N and Li Q Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
7- INACTIVATED p53 OR INCREASED ESTROGEN LEVELS OCCURING CONCOMITANTLY WITH BRCA1 INACTIVATION CONTRIBUTE TO BRCA 1 ASSOCIATED OVARIAN TUMOURIGENESIS.
Sara A. Rafferty*, Katherine V. Clark-Knowles, Jin-Yi Jiang, Laura Laviolette, and Barbara C. Vanderhyden
Dept. of Cellular and Molecular Medicine, University of Ottawa, and Centre for Cancer Therapeutics, Ottawa Hospital Research Institute

8- DIFFERENTIAL EFFECTS OF REPRODUCTIVE STEROID HORMONES ON OVARIAN CANCER PROGRESSION IN PRE VS POST-MENOPAUSAL OVARIES
Kendra Hodgkinson, Laura Laviolette, Carolina Perez-Iratxeta, Barbara C. Vanderhyden. Dept. of Cellular and Molecular Medicine, University of Ottawa. Centre for Cancer Therapeutics, Ottawa Hospital Research Institute

9- THERAPEUTIC TESTING OF A NOVEL PKC INHIBITOR GAP 107B8 ON OVARIAN CANCER CELLS
Fu Jian Yan, Isabella Steffensen, Kenneth Garson and Barbara C Vanderhyden
Dept. of Cellular and Molecular Medicine, University of Ottawa and Centre for Cancer Therapeutics, Ottawa Hospital Research Institute, Ottawa, ON, Canada

10-ESTROGEN TREATMENT INDUCES PRENEOPLASTIC LESIONS, ACCELERATES TUMOR ONSET AND DECREASES SURVIVAL TIME IN A TRANSGENIC MOUSE OF OVARIAN CANCER
Laura A. Laviolette, Kenneth Garson, Neha Minhas, Elizabeth A. Macdonald, Mary K. Senterman, Kerri Courville, Barbara C. Vanderhyden.
Dept. of Cellular and Molecular Medicine, University of Ottawa and Centre for Cancer Therapeutics, Ottawa Hospital Research Institute, Ottawa, ON, Canada

11- CHEMoresistant METASTIC GESTATIONAL TROPHOBLASTIC NEOPLASIA
S Petkiewicz¹, A Edgecombe¹, L Hopkins², V Acharya¹
Departments of Laboratory Medicine and Anatomical Pathology¹ and Gynecology Oncology²
12-HISTOPATHOLOGIC ASSESSMENT OF CHEMOTHERAPY EFFECTS IN EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING
T. Le 1 ; K. Williams 1 ; M. Senterman 1 , L. Hopkins 1 ; W. Faught 1 ; M. Fung Kee Fung 1
1- Dept of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Ottawa, Ottawa, Ontario

13-OMENTAL CHEMOTHERAPY EFFECT AS A PROGNOSTIC FACTOR IN OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING
Tien Le 1 ; Kona Williams 2 ; Mary Senterman 2 , Laura Hopkins 1 ; Wylam Faught 2 ; M. Fung Kee-Fung 1 1- Dept of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Ottawa, Ottawa, Ontario 2- Dept of Pathology and Laboratory medicine, University of Ottawa, Ottawa, Ontario

14-CORONAL SERAIL SECTIONING OF LUMPECTOMY SPECIMENS PROPOSED TECHNIQUE OF SECTIONING AND SUBMISSION OF TISSUE FOR MICROSCOPIC EXAMINATION OF BREAST CARCINOMA
MS Amin, C Bicamampuka, J Swift, BF Burns and KT Mai.
1Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada and 2Division of Surgical Pathology, The Ottawa Hospital, Ottawa, ON, Canada.

15- RADIOLOGICAL, CYTOLOGICAL AND HISTOLOGICAL CORRELATION IN BRONCHOALVEOLAR CARCINOMA
MS Amin1, C Morley2 and S Islam1,2.
1Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada 2Eastern Ontario Regional Laboratory Association, The Ottawa Hospital, Ottawa, ON, Canada.

16- LEFT VENTRICLE MESENCHYMAL HAMARTOMA: A NOVEL PRIMARY TUMOUR OF THE HEART
Scott H Bradshaw MD 1 , Paul Hendry MD FRCPS 2 , Munir Boodhwani MD FRCPS 2 , Carole Dennie MD FRCPC 3, John P. Veinot MD, FRCPC 1 , Division of Anatomical Pathology, Department of Pathology and Laboratory Medicine, 2. Division of Cardiac Surgery, Department of Surgery, 3. Department of Diagnostic Imaging, University of Ottawa, Ottawa, Ontario, Canada
17-DIFFUSE PULMONARY ALVEOLAR HEMORRHAGE IN MYELODYSPLASTIC SYNDROME
A Edgecombe¹, I Teo¹, H Sekhon¹,² & BF Burns¹,²
¹Department of Pathology & Lab Medicine, University of Ottawa, Ottawa ON
²Division of Anatomical Pathology, The Ottawa Hospital, Ottawa, ON

18-STAPHYLOCOCCUS LUGDUNENSIS PREVALENCE IN A PAEDIATRIC MICROBIOLOGY LABORATORY.
German, Greg¹, Bing Wang¹, Nancy Stewart², Robert Slinger¹,², and Frank Chan². ¹University of Ottawa, Department of Pathology and Laboratory Medicine ²Children’s Hospital of Eastern Ontario, Bacteriology Laboratory

19- ENDOMETRIOSIS AND OVARIAN CANCER
Arendas K, Elkeilani A, Singh SS
Department of Pathology and Laboratory Medicine, Department of Obstetrics, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada

20-CONCURRENT CHEMO RADIATION FOR THE TREATMENT OF PRIMARY VAGINAL CANCER
Bedy Lau, Rajiv Samant, Choan E, Victor Gallant and Tiffany Tam Department of Radiation Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, ON, Canada

21- PROGNOSTIC SIGNIFICANCE OF POST OPERATIVE MORBIDITIES IN ADVANCED EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY
Tien Le ¹; Ghadeer Alshaikh ¹; Laura Hopkins ¹; Wylam Faught ¹; Michael Fung Kee Fung ¹ Dept of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Ottawa, Ottawa Ontario

22-LEIOMYOMAS BEYOND THE UTERUS: UNUSUAL LOCATIONS, RARE MANIFESTATIONS AND IMAGING SPECTRUM
Najla Fasih, et al. Department of Diagnostic Imaging, The Ottawa Hospital, Civic campus, 1053 Carling Ave., Ottawa, ON K1Y 4E9, Canada. Recipient of Cum Laude award for the Educational exhibit at the 2006 RSNA scientific assembly.
23- THE IMPORTANCE OF OPTIMAL INGUINAL FEMORAL NODAL DISSECTION IN THE MANAGEMENT OF VULVA SQUAMOUS CELL CARCINOMA
Tien Le ¹, Ramadan Elsugi ¹, Laura Hopkins ¹; Wylam Faught ¹; Michael Fung-Kee-Fung ¹ ¹- Dept of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Ottawa, Ottawa, Ontario

24-SIGNIFICANCE OF CA125 RESPONSE IN EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING
T. Le ¹; L. Hopkins ¹; W. Faught ¹; M. Fung Kee Fung ¹
1- Dept of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Ottawa, Ottawa, Ontario
INTRACRANIAL MASQUERADE: A CASE REPORT

Hamidreza Faraji MD, John Woulfe MD PhD, FRCPC

Objective: To present unusual case of fortuitous meningioma containing unexpected pathology.

Case Presentation: This 73 y/o female was admitted for work up of fever of unknown origin. After being hospitalized for 4 days she was discharged home after non-contributory investigation. Two weeks later she returned with lethargy, loss of appetite, weight loss, sweating, vomiting, intermittent fever and right sided weakness. Her past medical history was remarkable for diabetes type 2, hypertension and anemia.

Results: Routine blood work showed mild leukocytosis with neutrophilia, Hgb 85 g/L; Hct 0.254; CRP: 117 mg/L; ESR: 135. Imaging studies including abdominal CT scan showed a homogenous soft tissue lesion in the left adnexa which was interpreted as a subserosal fibroid or adnexal mass. CT of the thorax showed evidence of AVM in the right middle lobe and also a right thyroid nodule. CT scan of the head showed a well circumscribed dural based lesion in the superior aspect of the left frontal lobe consistent with meningioma. The results of bone marrow aspiration and biopsy were consistent with anemia of chronic disease. The patient underwent brain surgery and a frozen section was requested. The diagnosis of malignant intravascular lymphoma, diffuse large B-cell type, within meningioma was made.

Discussion: According to the World Health Organization classification, intravascular lymphoma is a rare subtype of extranodal diffuse large B-cell lymphoma characterized by the presence of lymphoma cells only in the lumina of small blood vessels, particularly capillaries in the absence of an obvious extravascular tumor mass or leukemia. Intravascular lymphoma is extremely rare and difficult to diagnose in the live patient because of its nonspecific clinical signs. The most common clinical presentation is fever of unknown origin, skin rash, and mental status change or rapidly progressive neurologic signs (eg, dementia). The organs most commonly involved are the central nervous system, skin, lungs, kidneys, and adrenal glands, but virtually any site may be involved. Histopathologically large neoplastic lymphoid cells with prominent nucleoli and frequent mitotic figures occlude small vessel lumina. The tumor cells are immunoreactive for B-cell–associated antigens (eg, CD19, CD20, CD22, and CD79a). Combination chemotherapy with or without radiotherapy often is effective; many patients achieve complete remission, and long-term survival appears to be possible. Intravascular lymphoma has not, to our knowledge, been described within a meningioma. In this patient whether it is confined to this site or reflect disseminated, systemic disease, cannot be stated with certainty.

Conclusion: This case represents an unusual presentation of malignant intravascular lymphoma. The development of a meningioma producing neurological signs may have been fortuitous in this patient; permitting early detection and treatment of a far more ominous pathology.
INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM ARISING IN CYSTIC DYSTROPHY OF HETEROTOPIC PANCREAS

M. Marinescu MD, Bich N. Nguyen MD FRCPC. Department of Pathology and Laboratory Medicine, Ottawa Hospital, University of Ottawa

Introduction: Intraductal papillary mucinous neoplasm of the pancreas (IPMN) is characterized by neoplastic cells of the duct-epithelial lineage with abundant mucin lining of ectatic ducts. IPMNs have shown several histological variations and are classified in to 4 distinct types: gastric, intestinal, pancreato-biliary and oncocytic types. Recently, similar lesions have been reported in the biliary tree. On the other hand, cystic dystrophy of heterotopic pancreas (CDHP), also called paraduodenal/groove pancreatitis or hamartoma of the duodenum, is a heterotropic lesion arising in the vicinity of the vaterian system. The occurrence of both conditions in the same lesion has never been described.

Material and method: We report an exceptional case of CDHP, presenting as a duodenal polypoid lesion, in which an IPMN-like lesion with high-grade dysplasia is identified. Sections of the duodenal lesion were studied with mucin stains as well as immunostains.

Results: The patient is a 67-year-old man known for a 1 cm duodenal polyp located in D1. Previous biopsies showed an inflammatory lesion suggestive of peptic duodenitis. Because gross appearance of this polyp was very suspicious for malignancy, endoscopic resection was done. Microscopic examination shows a lesion mainly composed of dilated ducts, with fibromuscular proliferation, interstitial fibrosis and chronic inflammation in the background. The overall architecture of the lesion is consistent with CDHP. The epithelial lining is cuboidal to columnar with clear/mucinous cytoplasm, scattered goblet cells and focal oncocytic appearance. This is reminiscent of IPMN of the pancreas. There is high-grade dysplasia with papillary and cribriform architecture. By immunohistochemistry, the epithelial lining of CDHP, including dysplastic foci, shows positive staining for CK7, MUC5AC, MIB-1 and remain negative for MUC2, CK20 and CDX2. Adjacent duodenal mucosa is positive for MUC2 but negative for MUC1 and MUC5AC. The distinctive immunophenotype of the dysplastic foci is in favour of a lesion arising from the ductal elements of CDHP.

Conclusion: We described the first case of IPMN arising in cystic dystrophy of heterotopic pancreas. The fact that the duodenal wall often contains heterotopic pancreatic tissue may reflect the incomplete involution of the dorsal pancreas in this region. Occurrence of well defined neoplasms of the pancreas is therefore possible in ectopic pancreas.
BACKGROUND: There are no validated molecular biomarkers in EOC which correlate with prognosis or chemosensitivity. Breast cancer 1 (BRCA1) protein inactivation in sporadic EOC is common and reduced BRCA1 expression has been linked with platinum sensitivity. However, BRCA1 has not been clinically validated as a prognostic or predictive marker in EOC.

METHODS: The NCIC CTG-led Gynecologic Cancer Intergroup phase III trial, OV.16, compared topotecan/cisplatin followed by carboplatin/paclitaxel to standard carboplatin/paclitaxel in advanced EOC patients. With a median follow-up of 62 months (mo), there was no improvement in progression free survival (PFS) in the topotecan arm (Hoskins P, ASCO 2008). BRCA1 protein expression was determined by immunohistochemistry (IHC) on tissue microarrays of tumour samples from 251 Canadian patients (pts). IHC score was correlated with response rate (RR) and PFS using Cox proportional modeling adjusting for three independent prognostic factors identified in the main study (FIGO stage, residual disease (RD), and ECOG performance status). Preplanned subgroup analysis was performed for pts with minimal RD (microscopic or < 1 cm after debulking).

RESULTS: For the whole study group, BRCA1 score analyzed as a continuous variable showed no significant correlation between BRCA1 protein expression and PFS (adjusted HR = 1.15 [0.96, 1.37]; p = 0.12) or RR (HR = 0.89 [0.70, 1.12]; p = 0.32). In 116 pts with minimal RD, higher BRCA1 expression analyzed as a continuous variable was significantly associated with shorter PFS (HR = 1.40 [1.04, 1.89]; p = 0.03), but no significant correlation was found with RR. Exploratory analysis suggested that patients with minimal RD could be divided into low (BRCA1 ≤ 2.5) and high (BRCA1 > 2.5) expression groups. Pts with low BRCA1 expression had a longer PFS compared to those with high expression (median 24.7 and 16.6 mo, respectively; HR = 0.56 [0.35, 0.89]; p = 0.01).

CONCLUSIONS: This study suggests that BRCA1 protein is a prognostic marker in sporadic EOC patients with minimal RD. Further research is needed to evaluate BRCA1 as a predictive biomarker and to target BRCA1 expression to enhance chemotherapeutic sensitivity.
SUDDEN DEATH IN SPLENIC ARTERY SEGMENTAL MEDIOLYTIC ARTERIOPATHY

A Edgecombe1, I Teo1, M Marinescu1 & C Milroy1,2
1University of Ottawa, Department of Pathology & Lab Medicine, Ottawa, ON
2 Eastern Ontario Regional Forensic Pathology Unit, The Ottawa Hospital, Ottawa, ON

Background: Segmental mediolytic arteriopathy (SMA), a variant of fibromuscular dysplasia, is a rare non-inflammatory vascular disease. Mediolytic of the arterial media may be associated with aneurysm, dissection and stenosis. Visceral SMA primarily involves the branches of the celiac and superior mesenteric arteries and the middle-aged to elderly are typically afflicted. Potential complications include organ infarction and catastrophic intra-abdominal hemorrhage.

Design: A 20-year-old male had a nine-year history of type I diabetes, without diabetic complications. After retiring to bed one night, he suddenly cried out and collapsed. On arrival to hospital, vital signs were absent and resuscitation was unsuccessful. There was no evidence of illicit drug or alcohol abuse. His diabetes was well controlled with a recent haemoglobin A1c of 6.3%. A medico-legal autopsy was ordered.

Results: At autopsy, hemoperitoneum with 3000 ml of blood and clot was evident. The splenic artery was found to be ruptured 13 cm from the celiac artery origin. No other vascular anomalies were identified. Microscopically, there was segmental transmural mediolyis of the splenic artery media with extensive loss of the external elastica. Intima and internal elastica were focally absent. Extravasated erythrocytes were focally prominent within the media. Peri-adventitial inflammation was noted. The adjacent splenic artery had fibromuscular dysplasia. Neither vasculitis nor atherosclerosis was identified. Other vessels were normal.

Conclusions: Visceral SMA is a rare cause of fatal intra-abdominal hemorrhage. Isolated splenic artery SMA is exceedingly uncommon. The aetiology remains unknown. To our knowledge, we describe the youngest patient with visceral artery aneurysm and rupture associated with SMA. SMA of visceral arteries, therefore, must be included in the differential diagnosis of spontaneous intra-abdominal bleeding in all age groups.
TWO BROTHERS WITH LIPOID PROTEINOSIS TEMPORAL CLINICOPATHOLOGIC CORRELATIONS WITH HISTOPATHOLOGICAL AND ELECTRON MICROSCOPIC FINDINGS

J.S. Manusow\textsuperscript{1,2}, S. Brownstein\textsuperscript{1,2}, A. Samad\textsuperscript{3}, W.B. Jackson\textsuperscript{1}. \textsuperscript{1}Department of Ophthalmology and \textsuperscript{2}Department of Pathology, University of Ottawa, Ottawa, Ontario. \textsuperscript{3}Department of Ophthalmology, Dalhousie University, Halifax, Nova Scotia.

Purpose: To show the clinicopathological correlation between two brothers with lipoid proteinosis over time.

Methods: Clinical histories and examinations were compared and correlated to biopsy specimens taken over a period of sixteen years and analyzed by light and electron microscopy.

Results: An eighteen-year-old man presented with bilateral eyelid lesions since early childhood of unknown etiology. Past medical history included dysphonia, parotitis, and extensive dermatologic complaints. Slit lamp exam revealed discrete, confluent, waxy nodular lesions extending from the lashes to the mucocutaneous junction of all four lid margins. Dermatological examination showed extensive infiltrative papules and plaques, pock-like atrophic scars, finger nail clubbing, pearly nodules along the cuticular margins and thickening of the tongue. The patient had previously undergone extensive dermatologic work-ups and previous skin biopsies were performed at ages 2 and 6. His sixteen-year-old brother had similar, though less severe, findings. A diagnosis of lipoid proteinosis was first suggested only at the ophthalmological examination at age 18. Excisional biopsy specimens of the eyelid lesions revealed features of lipoid proteinosis by both light and electron microscopy. Previous skin biopsies at ages 2 and 6 disclosed early manifestations of these features, but were deemed non-specific at the time. In retrospect, these early onset microscopic findings became progressively more substantial as the patient grew older.

Conclusions: We present two cases of a very rare systemic disease. Despite previous dermatological evaluations including biopsies, the patients were not correctly diagnosed until they saw an ophthalmologist for their eyelid lesions. The temporal nature of the biopsies suggest that lipoid proteinosis is a progressive disease that evolves over time. Most ophthalmologists are not aware of lipoid proteinosis since there is a paucity of information in the ophthalmic literature. Ophthalmologists have the unique opportunity to diagnose this potentially fatal and cosmetically damaging condition by recognizing and biopsying the classic eyelid lesions and alerting a diagnostic pathologist to their concerns.
BREAK AND POSTER VIEWING (ATRIUM)
INTRACYSTIC ONCOCYTIC PAPILLARY RENAL NEOPLASMS: A VARIANT OF EPITHELIAL PAPILLARY NEOPLASMS DISTINCT FROM PAPILLARY RENAL CELL CARCINOMA.

H. Faraji, K.T. Mai. Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.

Background: We described 6 intracystic oncocyteic papillary renal cell carcinoma (IOPRCC) that were histopathologically and cytogenetically distinct from the common chromophil (papillary) renal cell carcinoma (RCC)

Method: IOPRCC were identified the Anatomical files at our institution and were further characterized with immunostaining for AMACR, CK7 and fluorescent in situ hybridization (FISH) for chromosomes 7, 17, Y and 3p (loci 3p 14 and 3p25)

Results: Of the total of 659 RCC, there were 6 IOPRCC, measuring 1.5 to 6 cm (2.4±1.1) occurring in patients with male: female ratio of 5:1 and ages of 46-73 years (57± 8). All tumors were not associated with distant metastasis or local recurrence in a period of follow-up from 1 to 12 years. The IOPRCC consisted of oncocyteic /eosinophilic cells forming characteristic papillae sparsely arranged and non-papillary architecture within the unilocular cysts. In 4 tumors, the neoplastic cells accounted for 30-50% of the cystic volume. The remaining two tumors displayed similar features in focal areas but occupied almost the entire cysts. The tumors displayed extensive foamy cytoplasm with or without focal clear cell changes in 4 cases. Capsular invasion was present in one case. Immunostaning was negative for progesterone receptor, cytokeratin 7, CD117 and carbonic anhydrase IX and positive for alpha-methylacyl-CoA racemase, vimentin, CD10 and RCC. FISH revealed no loss of chromosome 3p in all tumors and Y in all male patients and no trisomies of 7/17 in five tumors. On tumor (6 cm in diameter showed trisomies 7/17 in focal areas

Conclusions: IOPRCC is a distinct variant of RCC due to the favourable clinical behaviour, the intracystic proliferation of sparsely arranged oncocyteic papillae and the absence of chromosomal numeric changes of PRCC.
STUDY OF ENDOCERVICAL CURETTAGE SURGICAL PATHOLOGY SPECIMENS IN COLPOSCOPIC EXAMINATION

Farshid Siadat, Dr. Shahidul Islam
Department of Pathology and Laboratory Medicine, University of Ottawa, Ontario, Canada.
UTERINE MULLERIAN ADENOSARCOMA WITH CHONDROSARCOMATOUS OVERGROWTH: A CASE REPORT

A. Edgecombe and M. Kyrollos
Department of Pathology and Laboratory Medicine, The Ottawa Hospital, Ottawa, ON

**Background:** Mullerian adenosarcoma is a rare biphasic tumour composed of benign epithelial and malignant mesenchymal elements. It most commonly occurs in the uterus of post-menopausal women. An association with tamoxifen and oral contraceptives has been reported. While typical adenosarcomas are of low malignant potential, those with sarcomatous overgrowth have an unfavourable prognosis.

**Case Report:** A 43 year-old female presented to a peripheral institution. On ultrasound, tissue was seen prolapsing from the uterus. A biopsy was performed. Definitive surgical treatment included hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and omentectomy.

**Results:** Macroscopically, there was a polypoid lesion extending from the mid-uterus to the lower uterine segment measuring 5.5 x 2.5 x 2.0 cm. Microscopically, benign glands were dispersed throughout a malignant stroma with some glands demonstrating characteristic peri-glandular condensation of stromal cells (‘cuffing’). The malignant stroma was composed of a heterologous low-grade chondrosarcoma comprising greater than 75% of the stroma, thus meeting the criteria for sarcomatous overgrowth. The tumour invaded to the superficial myometrium. Ovaries, fallopian tubes, lymph nodes and omentum were unremarkable.

**Discussion:** Sarcomatous overgrowth occurs in 10% of cases and confers a prognosis similar to that of other high grade uterine sarcomas. Infrequently, sarcomatous overgrowth may involve heterologous elements, usually rhabdomyosarcoma. We report a rare uterine adenosarcoma with sarcomatous overgrowth of the heterologous chondrosarcoma component.
OCCULT CARDIAC AMYLOIDOSIS: A RARE CONTRIBUTOR OF POSTOPERATIVE DEMISE FOLLOWING CARDIAC SURGERY

T.A. Flood and J.P. Veinot. 1Anatomical Pathology, The Ottawa Hospital, Ottawa, Ontario, Canada.

Background: Cardiac amyloidosis is an uncommon disorder that occurs when fibrillar proteins are deposited in the myocardium and/or coronary artery walls and leads to abnormalities in contraction and conduction. Patients with cardiac amyloidosis can present with angina, symptoms of myocardial infarction, or sudden death. We present two patients who underwent cardiac surgery whose postoperative courses were complicated by poor cardiac output and eventual death. Autopsies showed previously undiagnosed severe cardiac amyloidosis.

Design: Patient#1: 52 year old man admitted for triple CABG following coronary in-stent restenosis. Postoperative course was complicated by low cardiac output requiring inotropes and an intra-aortic balloon pump. Further complications included atrial fibrillation, sepsis, and hepatic and renal insufficiency. On postoperative day 26 the patient suffered a fatal cardiac arrest.

Patient#2: 86 year old man admitted for aortic valve replacement and CABG. His post-operative course was complicated by right ventricular failure, sinus ventricular tachycardia and left ventricular dysfunction for which he required prolonged inotropic support. He developed bilateral pleural effusions and a mediastinal soft tissue abscess. On postoperative day 32 the patient went into asystole and died.

Results: Patient#1: Heart weight was 575g and all coronary artery bypass grafts were intact and uncomplicated. There was extensive myocardial involvement by amyloid. Amyloid deposits were also observed within the walls of epicardial arterioles and in the vein grafts. Moderate deposition of amyloid was detected systemically. The amyloid was AL type and an underlying plasma cell dyscrasia was identified.

Patient#2: Heart weight was 550g and the aortic valve prosthesis was uncomplicated. Coronary artery bypass grafts were intact and patent. There was moderate to severe amyloid involvement in the myocardium of all chambers. Amyloid also involved the visceral vessels (pulmonary arteries and veins) and was the senile type.

Conclusion: Occult cardiac amyloidosis is an infrequently described entity that can contribute significantly to postoperative morbidity and mortality. There are no specific clinical signs or symptoms that are associated with this disorder. Prior cardiac surgery can cloud the clinical picture because many of the observed signs and symptoms can be attributed to postoperative sequelae. These cases demonstrate a rare but potentially fatal condition that can be considered in postoperative cardiac surgery patients who are doing poorly.
EXPRESSION PROFILE OF P16 (INK 4A) AND MIB1 (KI-67) IN HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) AND IMMATURE SQUAMOUS METAPLASIA (ISM) OF THE UTERINE CERVIX

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Background: Recognition of HSIL from ISM can be a very difficult task, particularly in those cases with "borderline" morphologic features. The p16 gene product inhibits progression of the cell cycle. Integration of the HR-HPV DNA into the genome however activates a positive feedback loop that paradoxically elevates p16 proteins in cervical dysplasia and carcinoma. MIB1 (Ki-67) is expressed in the nucleus of cells that are no longer in G0 phase of the cell cycle.

Objective: The purpose of the current study was to examine p16 and MIB1 expression profile and cellular localization in HSIL and ISM of the uterine cervix.

Methods: Immunohistochemistry was done with commercially available monoclonal antibodies against p16 and MIB1 on 150 cases of HSIL and 150 cases of ISM. Reactivity to p16 was scored as negative (no immunoreactivity), focal positive (<5% of cells) and diffuse positive (>90% of cells). MIB1 expression was assessed in the basal, parabasal and intermediate keratinocytes. Intensity of staining was graded as weak, intermediate or strong. Localization was categorized as cytoplasmic, nuclear or combined. Assessment of immunostains was confirmed with 2 independent pathologists.

Results: All 150 (100%) cases of HSIL showed diffuse and strong nuclear and cytoplasmic staining of p16. In all HSIL, MIB1 expression was strong with nuclear staining seen in basal, parabasal and intermediate cells. In 30 (20%) cases of ISM, p16 immunostain was focally positive with weak nuclear staining. Additional 15 (10%) cases showed a weak cytoplasmic p16 staining. All 150 (100%) cases of ISM showed strong nuclear staining for MIB1 in the basal keratinocytes.

Conclusion: Diffuse and strong nuclear and cytoplasmic p16 expression in combination with strong MIB1 nuclear expression in basal, parabasal and intermediate cells favor HSIL over ISM.
LUNCH AND POSTER VIEWING

(ATRIUM 2ND FLOOR, FACULTY OF MEDICINE)
GUEST SPEAKER
DR. WENXIN ZHENG

UNIVERSITY OF ARIZONA, COLLEGE OF MEDICINE
TITLE: ENDOMETRIAL PRECANCER AND CARCINOGENESIS
DIRECT mecA PCR TESTING FROM BLOOD CULTURE BOTTLES WITH GRAM POSITIVE COCCI IN CLUSTERS AND RETROSPECTIVE ANALYSIS OF ANTIBIOTIC USE

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Division of Microbiology, Department of Pathology and Laboratory Medicine, The Ottawa Hospital

Objective: Detection of oxacillin resistance (OXR) in Staphylococcus spp. from positive blood cultures requires a minimum of 24-48 hour compared to less than 2 hours for mecA by PCR. Early detection of OXR in Staphylococcus spp. can impact therapeutic management. We evaluated the accuracy of the mecA PCR from positive BACT/Alert blood culture bottles (direct mecA PCR) with gram positive cocci in clusters (GPCC) and assessed the potential for change in antibiotic usage.

Methods: Direct mecA PCR was performed in the positive blood cultures with GPCC by Roche Light-Cycler MRSA Kit. Susceptibility testing of the staphylococcal isolates was performed using the Vitek 2 (BioMérieux). A retrospective analysis of antibiotic usage at the time of the initial blood culture report was performed from randomly selected patients from July - December 2009.

Results: A total of 243 positive blood cultures with GPCC were tested, including 24 MRSA, 72 MSSA, 97 OXR and 50 OXS coagulase negative staphylococci (CoNS) by Vitek 2. The direct mecA PCR detected all of MRSA and MSSA. It also correlated with the Vitek 2 results in 137/147 (93%) CoNS isolates. The direct mecA PCR had sensitivity, specificity, PPV and NPV of 96, 88, 94 and 92%, respectively. A total of 84 bacteremias (40 S. aureus, 44 CoNS) were reviewed for the antibiotic usage—result in table.

Conclusion: The direct mecA PCR correlated well with the Vitek 2 result. The discrepancies between the direct mecA PCR and Vitek 2 results have to be resolved. The direct mecA PCR assay has the potential to initiate earlier changes in antibiotic therapy.

<table>
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<td>6</td>
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<td>17</td>
<td>16</td>
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<tr>
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Background: Follicular lesions (FL) of the thyroid encompass non-neoplastic and neoplastic conditions. Diagnosis of follicular lesions is a challenging area, in the interpretation of thyroid FNAB.

Objectives: The purpose of the study is two fold: 1. To identify cytologic features that will more accurately predict follicular neoplasia (FN). 2. To recognize diagnostic pitfalls in the differential diagnosis of follicular lesions (FL).

Design: A computer database search was performed for diagnosis of FL and indeterminate for neoplasia on FNAB of thyroid, between January 2003 and August 2008 from the archives of the Cytology section at Ottawa Hospital. A total of 504 cases with a cytological diagnosis of FL were retrieved. 205 cases (40.6%) had histological follow-up and were retained for the study.

Results: Histological follow-up of 205 cases showed follicular adenoma (FA) in 53 (25.8%), Hirthle cell adenoma (HA) in 19 (9.2%), multinodular goitre (MGN) in 95 (46.3%), papillary carcinoma, follicular variant (PTCFV) in 25 (12.2%), thyroiditis (THY) in 8 (93.9%) and follicular carcinoma (FC) in 5 (2.4%) of patients. Cytological features that accurately predict FA (48 specimens, 91%), FC (4 specimens 80%) and PTCFV (23 specimens, 92%), consist of tight microfollicle formation present in > 60% of the smear area and scant to nil colloid in the smear background. Another important cytological feature that was found in this study is the presence of nuclear grooves in more than 5% of follicular cells which predict a neoplastic lesion. However presence of nuclear grooves in more than 30% of follicular cells is predictive of papillary carcinoma. Nuclear grooves in more than 5% of follicular cells were found in FA (16 specimens, 30%), FC (2 specimens, 40%) and PTCFV (16 specimens, 64%), on FNAB. The most common diagnostic pitfall is follicular cells wrapped up in clotted blood and endothelial cells (MGN, 87 specimens).

Conclusion: The cytological features that will increase diagnostic specificity of FN (FA, FC and PTCFV) are tight microfollicle formations present in >60% of the smear, nuclear grooves in > 5% of follicular cells and scant colloid in the smear background. The most common diagnostic pitfall is clotted blood.
BREAK AND POSTER VIEWING (ATRIUM)
LUPUS NEPHRITIS: CLASSIFICATION REVIEW WITH CLINICOPATHOLOGIC CORRELATION IN PREDICTING RENAL OUTCOME

Hamidreza Faraji MD, Akram Elkeilani MD, FRCPC, Susan Roberston MD, FRCPC

Objective: To compare the ability to predict worsening renal function for lupus glomerulonephritis when using the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 versus the World Health Organization (WHO) classifications. As the major differences include subclassifications of segmental (S) versus global (G) involvement, active (A) versus chronic(C) processes, and the presence or lack of superimposed membranous (Class V) process on a primary class 3 or 4 disease; these variables were specifically examined for predictive ability. A comparison with Austin activity and chronicity indices was also examined in anticipation that this might mirror A/C or S/G designations in the ISN/RPS classification.

Methods: The study group includes 30 patients with renal biopsies done between 2003-2008, for whom serum creatinine at presentation and at 1 year follow-up was available. Serum creatinine change over one year was looked at as both a continuous variable as well as a categorical variable (stable/improved versus worsened). An attempt was made to develop a predictive model for deteriorating renal function using multiple regression entering age, creatinine at presentation, primary class designation (I- VI), addition of secondary class V, S versus G designation, A versus C designation, Austin activity & chronicity indices.

Results: This group of 30 patients (27 females) with a mean age of 36.3 (18-69) had a primary class distribution of 0% Class I (minimal mesangial), 3% Class II (mesangial proliferative), 7% Class III (focal proliferative), 43% Class IV (diffuse proliferative) and 13% Class V (membranous) and 3% class VI (advanced sclerosing). With this population the sample size was too small to develop a predictive model for further testing. Analysis of the important variables for correlation with change in serum creatinine did show the expected correlation (Pearson) with primary stage designation (p=.03) as well as with separate designation of class IV as S (20%) versus G (23%) disease (p=.049). Separate classification of glomerulonephritis as A or C and Austin activity/chronicity indices showed no correlation with worsening serum creatinine although there was a trend with respect to C class (p=.06). Age at presentation and initial creatinine were not predictive in this population. Despite the correlation seen using change in serum creatinine as a continuous variable, a chi square test of class IV-S nephritis versus Class IV-G nephritis showed no significant difference between these groups with respect to worsening renal function (p=.06) although a trend was present for a worse outcome in the IV-G group. This difference could not be explained by association with other variables (chronicity or activity indices or classes).

Conclusion: A correlation with renal outcome was found when Class IV lupus nephritis was subclassified into IV-G and IV-S as recommended by (ISN/RPS) 2003 classification system. Although the literature to date on this issue is mixed, in this small sample a trend was found for increased serum creatinine in the IV-G group. From this study this is not easily linked to other variables. Weaknesses of this study include a limited population size and lack of information on treatment used which should be addressed by extending the study prospectively.
AWARDS TO BE ANNOUNCED
POSTERS
REGULATION OF APOBEC3G-MEDIATED INTRINSIC IMMUNITY TO HIV INFECTION

Kasandra Bélanger, Halil Aydin, Olga Agah and Marc-André Langlois

Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa.

APOBEC3G is a host-encoded antiretroviral protein that can deaminate cytosines into uracils in single-stranded DNA replication intermediates. In dividing cells however, APOBEC3G is mostly maintained in a catalytically inactive state because of the binding of various cellular RNAs and proteins that sequester APOBEC3G into high molecular mass (HMM) complexes. Our goals are to identify these cellular factors responsible for the inactivation of APOBEC3G and to disrupt their interaction in order to extend the antiretroviral activity of APOBEC3G to dividing cells, such as activated T-cells. To map the sites on APOBEC3G that interact with regulatory elements, we generated several point and deletion mutants of the protein. These mutants were analyzed for the loss of HMM complex assembly by velocity sedimentation followed by Western blot analysis. We found that the C-terminal domain alone of APOBEC3G is not sufficient for HMM complex formation and that the N-terminal domain of the protein is required for the assembly of these complexes. Based on structural and functional studies, we then targeted specific amino acid residues potentially involved in HMM complex assembly and identified tryptophan 92 which is part of a SWS motif at the N-terminus. Mutating this tryptophan into an alanine prevented the formation of HMM complexes without affecting protein stability or its antiretroviral activity. It thus appears that the region encompassing the N-terminal SWS motif may have an important role in modulating the activity of APOBEC3G in dividing cells.
SMALL MOLECULE ENHANCERS AND SKELETAL MYOGENESIS

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¹-Honours Biomedical Sciences Program, Faculty of Science, University of Ottawa
²-Dept. of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa

Small molecules such as retinoids and rexinoids are potent inducers of skeletal myogenesis through their action on the nuclear retinoid receptors, Retinoic Acid Receptor (RAR-α, β, and γ) and Retinoid X Receptor (RXR-α, β, and γ), which function as ligand-inducible transcription factors that mediate skeletal myogenesis via upregulation of the expression of myogenic regulatory factors (MRFs). It is purported that RAR/RXR heterodimers transduce the retinoid signal, but only ligand binding to the RAR can activate the RAR/RXR heterodimer to induce skeletal myogenesis, while ligand binding to the RXR alone is not sufficient for activation. However, our lab has shown that an RXR-selective synthetic ligand (“rexinoid”), LGD1069, can specifically activate the RAR/RXR heterodimer. Moreover, we hypothesized that RXR-selective ligand (LGD1069/LGD) can induce skeletal myogenesis without activation of RAR, and experiments using 19 murine embryonal carcinoma and a mutant P19 subclone (RAC65) with a dominant negative mutation encoding the RAR-α gene, were conducted to validate our hypothesis. It was found that the RXR-selective ligand LGD1069 induces skeletal muscle differentiation in P19 and RAC65, as confirmed by immunofluorescence microscopy and quantification of % differentiation. Western Blot analysis reveals the MRF myogenin is expressed by Day 9 in P19 in LGD-treated conditions (RAC65 in progress) and RXR-α is expressed in a similar pattern in both P19 and RAC65. Further work will be completed to determine the expression of RAR-α in P19 and RAC65. Presently, it is possible to conclude that RXR-selective ligand can induce formation of skeletal muscle independent of RAR activation, suggesting a possible novel role for RXRs in skeletal myogenesis.
RETINOID X RECEPTORS PLAY A KEY ROLE IN SKELETAL MUSCLE DEVELOPMENT

Melanie Le May, Qiao Li
Departments of Pathology and Laboratory Medicine, and of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa.

Vitamin A is essential for proper embryonic development. Both natural and synthetic retinoids are powerful regulators of cell growth and differentiation and treatment of tissue cultures with these compounds induces differentiation into different cell lineages. Retinoic Acid (RA) induces skeletal muscle differentiation by activating the retinoid receptors which regulate cellular differentiation through binding to enhancers or promoters of the genes that they govern. RA can bind to both the Retinoic Acid Receptor (RAR) and the Retinoid X Receptor (RXR) and is believed to exert its effects through RAR/RXR heterodimers. It is currently unknown how much the RXR contributes to RA induced differentiation. Preliminary results in our lab using embryonal carcinomal cells and an RAR selective ligand demonstrate that activation of RARs alone does not achieve the level of skeletal enhancement that RA does. Using a selective ligand to activate RXR alone not only achieves greater enhancement than RA, but as the dose of RXR treatment increases, there is a concomitant decrease in cardiac muscle. Our preliminary data using embryonic stem cells is promising and has confirmed that RXRs are the key to inducing skeletal muscle. We hypothesize RXR is required and is an important contributor, if not the key player, in skeletal muscle differentiation. These results will allow us to uncover novel pathways of RA signalling and to elucidate whether RXR is acting alone, as a homodimer, or in conjunction with RAR as a heterodimer as well as the target genes of the RXRs involved in myogenesis. Further down the line it may help us understand the requirements to grow and regenerate skeletal muscle for devastating diseases like muscular dystrophy if we can direct pluripotent cells into specification of the muscle lineage. Finally, in better understanding how to force proliferating cells to differentiate, it may be possible to generate more potent anti-cancer treatments with fewer side effects.
NOVEL MULTIVALENT HIV PEPTIDES AND LIPOPEPTIDES INDUCE A STRONG CELL MEDIATED IMMUNE RESPONSE IN MICE.

Authors: Haitham T. Ghunaim, Francisco Diaz-Mitoma, Jose Torres, Ashok Kumar, David E. Anderson, and Ali Azizi.

Abstract:
The nature of the immune response required for protection from HIV is not clear. Strong innate and adaptive immune responses at mucosal and systemic levels elicited by a vaccine might be able to control HIV infection. The genetic hypervariability of HIV remains a major obstacle for developing an effective vaccine. Designing immunogens that can elicit immune responses against the genetically varied circulating isolates of HIV presents a key challenge for creating an HIV vaccine. Through bioinformatic approaches; our group has developed an innovative multivalent HIV vaccine comprised of a pool of lipopeptides representing variable regions of Env and Gag-HIV-1 proteins (Azizi et al., J Immunol 180, 2174-2186; 2008). Once designed, many antigenic variants of a given epitope were synthesized simultaneously, which collectively represents much of the in vivo variability seen in an epitope. When tested in non-human primates these antigens elicited a strong cell-mediated immune response against various HIV subtypes. In this study, the breadth, potency and longevity of the vaccine-induced humoral and cellular immunity in mice are evaluated. First the ability of each set of peptides to elicit an immune response after subcutaneous immunization was tested. Thirteen groups of C57B6 mice were immunized 3 times using a 100 μg/dose of peptides for each. Poly I:C was used an adjuvant to augment the cell-mediated immune response at 100 μg/dose. Blood was collected from the saphenous vein before and after each immunization. Two weeks after the last immunization, mice were euthanized and spleens were collected. Cell-mediated immune responses were measured using intracellular cytokine staining (ICS), ELISPOT, [H3] thymidine incorporation, and Th1/Th2 cytokine array. A strong CD4+ and CD8+ responses have been observed in the groups that received either Gag or Env peptides or lipopeptides compared to controls. Stimulation with the corresponding peptide or lipopeptides has induced several cytokines, mainly IFN-γ. IFN-γ production in CD3+CD8+ increased by 2-8%, and in CD3+CD4+ by 1.5-12% as detected by ICS. IFN-γ was also produced by splenocytes stimulated with the peptides or lipopeptides as detected using ELISPOT. These studies will help identify the role of each peptide/lipopeptides in the production of an immune response.
ROLE OF THE 26S PROTEASOME IN THE ACTIVATION OF RETINOIC ACID RESPONSIVE GENES

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Departments of Pathology and Laboratory Medicine and of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Retinoic acid (RA) is the most potent derivative of vitamin A. It is involved in many biological processes including development, haematopoiesis, bone formation, vision, cell growth, differentiation and apoptosis. Therapeutically, RA has been recognized as an anti tumour agent in certain malignancies such as leukemia, prostate, oral and skin cancers. RA has also been used to reverse pre malignant lesions in lung, breast and liver cancers and to prevent the incidence of second primary tumours in head and neck cancer patients. The physiological effects of RA are mediated through the action of both retinoic acid receptor (RAR) and retinoid X receptor (RXR). These receptors mediate the expression of a set of genes that require the function of transcriptional coactivators (such as SRC-1 and p300) as well as corepressors (such as N-CoR). It has been reported that the activity of the 26S proteasome plays a fundamental role in retinoid receptor-mediated transactivation. However, the mechanism underlying this role remains unclear and needs to be investigated. In this study, we discovered the impact of the 26S proteasome function on the occupancy of RA-responsive promoters by RAR, RXR, SRC-1, p300, N-CoR and RNA polymerase II through chromatin immunoprecipitation (ChIP) assays. We used RARB2 and CYP26A1 gene promoters in P19 embryonic carcinoma cells for ChIP assays. These genes are considered two of the best studied RA responsive genes. We also analyzed the effect of the proteasomal activity on the interaction of endogenous RAR with its cofactors by performing coimmunoprecipitation assays. Additionally, we examined the effects of RA on the ubiquitination and turnover of retinoid receptors. Taken together, our data suggests that the 26S proteasome is a crucial factor regulating the formation of protein complexes that bind to retinoid responsive promoters and that this occurs in mechanisms other than the proteolytic function of the proteasome. We believe that this study will enhance our understanding of the molecular basis underlying the function of the 26S proteasome in activating RA-responsive genes. Furthermore, it will shed new light on the role of ubiquitination in transcriptional regulation.
ROLE OF HISTONE ACETYLTRANSFERASE ACTIVITY IN THE SPECIFICATION OF CARDIOMYOCYTE LINEAGE

Mach H, Lacroix N and Li Q
Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

Coronary artery disease and congestive heart failure are the leading causes of death for both men and women worldwide. Among them, ischemic heart diseases are the primary cause of mortality. Cell replacement therapy using various types of stem cells holds great promise for treating these ischemic heart diseases. Many obstacles must be overcome before stem cells can be used in mainstream therapies with the primary obstacle being the efficacy with which stem cells can differentiate into cardiomyocytes.

Cardiac muscle development is a complex process arranged by a group of cardiac muscle transcription factors such as GATA4, MEF2C and Nkx2-5 which are expressed in cardiac muscle precursor cells and then act synergistically to activate cardiac muscle gene program. A transcriptional coactivator, p300, capable of histone acetyltransferase (HAT) activity also plays a major role in cardiomyogenesis. Mice lacking p300 exhibit defects in heart development and reduced amount of contractile proteins in the fetal heart. GATA4 and MEF2C are dependent on p300 HAT activity to carry out their full capacities as transcription factors.

To determine the role of p300 HAT activity in cardiomyogenesis, we took an inhibitor approach using curcumin, a cell-permeable compound extracted from *curcuma longa rhizome*, as an inhibitor of p300 HAT activity. We show that curcumin not only inhibits cardiomyocyte specification, but also affects cardiac muscle development. Curcumin also blocks gene expression of cardiac muscle regulator GATA4 and MEF2C in early stages of cell specification and inhibits Nkx2-5 and cardiac Troponin-T expression in later stages of cardiomyocyte development. Conversely, targeting histone deacetylase (HDAC) activity with HDAC inhibitors, such as valproic acid, induces cardiomyocyte specification and development.

Our data suggests that p300 HAT activity plays distinct roles at different stages of cardiomyocyte specification and development, causing hierarchical expression of cardiac transcription factors; these effects may be a direct result of chromatin modification. Deciphering the molecular basis for the role of p300 HAT activity in cardiomyogenesis will be vital for reprogramming mature cells or directing differentiation of stem cells to repair damaged hearts in cell replacement therapy and cardiovascular regenerative medicine.
INACTIVATED p53 OR INCREASED ESTROGEN LEVELS OCCURRING CONCOMITANTLY WITH BRCA1 INACTIVATION CONTRIBUTE TO BRCA1-ASSOCIATED OVARIAN TUMOURIGENESIS.

Sara A. Rafferty, Katherine V. Clark-Knowles, Jin-Yi Jiang, Laura Laviolette, and Barbara C. Vanderhyden
Dept. of Cellular and Molecular Medicine, University of Ottawa, and Centre for Cancer Therapeutics, Ottawa Hospital Research Institute

Loss-of-function BRCA1 mutations increase the risk of epithelial ovarian cancer and, in both humans and mice, preneoplastic morphologic changes in the ovarian surface epithelium (OSE) occur more often in ovaries in which BRCA1 is inactivated versus intact. However, the inactivation of Brca1 in murine OSE does not cause tumour development, suggesting additional molecular changes are required for ovarian tumourigenesis. The inactivation of p53 is one such candidate, as it is found in 60% of BRCA1-associated tumours and increases proliferation of cells with mutated BRCA1 by disabling cell cycle checkpoints. Hormonal factors may also promote Brca1-associated tumourigenesis, since exogenous estradiol promotes preneoplasia in mammary tissue of mice with mammary-specific loss of Brca1. The hypothesis of this study is that p53 inactivation or increased estrogen act concurrently with Brca1 inactivation to promote ovarian tumourigenesis. The effect of p53 was investigated by inactivating Brca1 and p53 alone or in combination in the OSE of conditional knockout mice. Compared to the inactivation of p53 alone, the additional loss of Brca1 accelerated tumour progression in vivo and increased OSE anchorage-independent growth in vitro. The role of estrogen was explored by implanting a 60-day timed-release pellet containing 0.25mg estradiol or placebo in mice with Brca1 conditionally inactivated in the OSE. Preneoplastic morphologic changes in the OSE were examined 60 and 180 days after pellet insertion and revealed a significantly higher percentage of OSE exhibiting columnar morphology and hyperplasia with estrogen treatment. The number of epithelial invaginations was also significantly increased after 60 days (P < 0.05). A direct relationship between Brca1 and estrogen was established when the inactivation of Brca1 in primary granulosa cells in vitro resulted in significantly increased FSH-induced aromatase expression and estradiol secretion. These results suggest that inactivation of p53 or increased estrogen levels occurring concomitantly with Brca1 inactivation contribute to Brca1-associated ovarian tumourigenesis.
DIFFERENTIAL EFFECTS OF REPRODUCTIVE STEROID HORMONES ON OVARIAN CANCER PROGRESSION IN PRE VS POST-MENOPAUSAL OVARIES

Kendra Hodgkinson, Laura Laviolette, Carolina Perez-Iratxeta, Barbara C. Vanderhyden. Dept. of Cellular and Molecular Medicine, University of Ottawa. Centre for Cancer Therapeutics, Ottawa Hospital Research Institute

Epithelial ovarian cancer is often asymptomatic during its initial stages and due to a lack of effective early screening methods, the disease is frequently diagnosed at advanced stages. Identification of causative factors is valuable for the development of preventative measures and early treatment options. Epidemiological studies have demonstrated that women who take hormone replacement drugs after menopause have an increased risk of developing ovarian cancer. This study uses two mouse models of ovarian cancer to evaluate the impact of steroid hormones on ovarian cancer progression, particularly after menopause, when the majority of ovarian cancer is diagnosed. In this survival study, 17-β estradiol (E2) treatment in vivo decreased the length of survival in ovariectomized SCID mice xenografted with murine ovarian cancer cells. Treatment with E2 in vitro did not affect proliferation of the cancer cells or mouse ovarian surface epithelial cells. Microarray analysis of the tumours has revealed significant upregulation of 196 genes and downregulation of 55 genes in animals treated with exogenous E2, including genes involved in cell differentiation, proliferation and migration. To model the development of ovarian cancer in a menopausal ovary, menopause will be induced in the tgLS-CAG-TAg transgenic mouse model of ovarian cancer by vinylcyclohexene diepoxide (VCD) treatment prior to oncogene activation. Preliminary results suggest that the menopausal mice tend to have prolonged survival and altered tumour histology relative to non-menopausal mice. Current experiments are exploring the impact of E2 and progesterone treatment on disease progression in this model. Elucidation of the molecular pathways altered by E2 will improve our knowledge of the etiology of ovarian cancer and may lead to advances in the prevention, early detection or treatment of the disease.
THERAPEUTIC TESTING OF A NOVEL PKC INHIBITOR GAP 107B8 ON OVARIAN CANCER CELLS

Fu Jian Yan, Isabella Steffensen, Kenneth Garson and Barbara C Vanderhyden Dept. of Cellular and Molecular Medicine, University of Ottawa and Centre for Cancer Therapeutics, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Background: Ovarian cancer is the most fatal gynaecologic disease in the western world. In 2009 in North America, an estimated 23,896 women will develop ovarian cancer and an estimated 15,240 women will die from this disease. Current treatments are limited to surgery or chemotherapy, but the disease often recurs. Thus, the development of novel cancer therapeutics remains important. The protein kinase C (PKC) family of serine/threonine kinases is involved in cellular proliferation, differentiation, apoptosis and cell polarity. One PKC isoform, PKC iota, has recently been identified as a human oncogene and has been shown to be overexpressed in serous epithelial ovarian cancers and is thus a potential therapeutic target for ovarian cancer.

Objective: We have tested a novel PKC inhibitor GAP-107B8 (PharmaGap Inc., Ottawa) in vitro on a panel of nine ovarian cancer cell lines to determine its potential to inhibit cell proliferation, proliferation in soft agar, and migration.

Methods: Nine ovarian cancer cell lines were treated with three different concentrations of GAP-107B8 and then screened using high throughput assays to measure the proliferation of cells in adherent and anchorage independent (soft agar) cultures. The ability of cells to migrate in the presence of GAP-107B8 was also determined.

Results: We observed significant reduction in cell proliferation in 6 of 9 ovarian cancer cell lines tested, including two cell lines resistant to the standard chemotherapy. GAP-107B8 inhibited cell proliferation by 30% to 79% compared with untreated cells, with more than 50% inhibition in 4 of 7 cell lines. Treatment with GAP-107B caused a reduction in growth in soft agar in 7 of the 9 cell lines tested in vitro. GAP-107B8 inhibited growth in soft agar by 50% to 94% compared with untreated cells, with 80% or greater inhibition in 6 of 7 cell lines. Finally, 5 of 8 cell lines tested showed significant inhibition of mobility following treatment with GAP-107B8. There was 50% or greater inhibition in all 5 cell lines compared with untreated cells. Flow cytometry indicated that treatment with GAP-107B8 appeared to increase the proportion of sub-G1 (apoptotic) cells as well as the proportion of cells in the G2/M stage of the cell cycle. TUNEL staining suggested an increased number of apoptotic cells after GAP-107B8 treatment.

Conclusion: The novel PKC inhibitor GAP-107B8 displays good efficacy in vitro in suppressing several cancer cell characteristics in a variety of ovarian cancer cell lines, possibly by causing cells to undergo apoptosis. Further experiments are underway to investigate the therapeutic potential of GAP-107B8 in xenograft models of ovarian cancer.
ESTROGEN TREATMENT INDUCES PRENEOPLASTIC LESIONS, ACCELERATES TUMOR ONSET AND DECREASES SURVIVAL TIME IN A TRANSGENIC MOUSE OF AVARIAN CANCER

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The majority of ovarian cancers are thought to arise from the ovarian surface epithelium (OSE), but the disease often goes undetected in its early stages therefore the factors that contribute to its etiology remain poorly understood. The primary objectives of this study were to determine the role of the female reproductive steroid hormones (17β-estradiol (E2) and progesterone (P4)) on the initiation and progression of ovarian cancer. A transgenic mouse model was developed to examine the effects of the steroid hormones on ovarian tumorigenesis. The mouse model (tgCAG-LS-TAg) utilizes the Cre-LoxP system to inducibly express the oncogene SV40 large T-Antigen (TAg) in the OSE following the intrabursal injection of adenovirus expressing Cre recombinase (AdCre). tgCAG-LS-TAg mice receiving AdCre (n=11) developed primary ovarian tumors, metastases to other tissues including the uterine horns, liver and diaphragm, and 64% developed ascites. The mice had a median survival time of 113 days post-intrabursal injection. An analysis of the ovaries from mice injected with AdCre and euthanized at early time points revealed a long latency from the time of TAg expression in the OSE (~ day 7) until the presence of tumors (between days 85-90). In order to examine the effects of the steroid hormones on ovarian tumorigenesis, mice underwent prolonged exposure to either exogenous E2 (0.25 mg/pellet) or P4 (50 mg/pellet) via the subcutaneous insertion of 60-day slow-release pellets at the same time as the intrabursal injection of AdCre. Treatment with P4 (n=11) did not affect survival, tumor burden, or incidence of ascites. Treating mice with exogenous E2 (n=11) significantly decreased the median survival time compared to the mice not treated with hormones (50 days vs. 113 days, respectively). Control tgCAG-LS-TAg mice injected with an adenovirus expressing eGFP (AdGFP), with or without hormone treatment, were disease-free for at least 365 days post-surgery. Mice treated with AdGFP + E2 that were euthanized at early time points (day 30, 45, and 60 post-intrabursal injection) had an increase in putative preneoplastic lesions on the ovarian surface (columnar cells, hyperplasia). These results demonstrate that E2 exposure alone is unable to induce ovarian cancer. However, once tumorigenesis is initiated (AdCre), treatment with exogenous E2 results in an earlier onset of ovarian tumors, thus decreasing the overall survival time of the mice.
CHEMORESISTANT METASTIC GESTATIONAL TROPHOBLASTIC NEOPLASIA

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Background: Gestational trophoblastic neoplasia (GTN) may result from any gestational event in which there is neoplastic transformation of trophoblastic cells¹. The majority of women with GTN are cured by treatment with chemotherapy, however, a small percentage of cases of GTN will be resistant to chemotherapy and will require surgical intervention and more aggressive chemotherapeutic regimens.

Clinical history: We present the case of a 44 year old woman with a chemoresistant hydatiform mole and pulmonary nodules. Surgical management and multi-agent chemotherapy resulted in return of βhCG levels to normal after 4 months.

Results: Gross examination revealed bulky uterus containing vesicle-like structures. Histological examination of the uterus demonstrated an invasive mole with myometrial invasion and a large intravascular component, consistent with invasive hydatidiform mole. There was no breach of the serosa.

Discussion: Chemoresistance occurs in less than 5% of low-risk GTN. The diagnosis was made based on examination of hematoxylin and eosin stained sections from the hysterectomy.
HISTOPATHOLOGIC ASSESSMENT OF CHEMOTHERAPY EFFECTS IN EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING

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Objectives: To assess the prognostic significance of tumour induced immunologic reactions and pathologic tumour response to neoadjuvant chemotherapy.

Methods: Retrospective chart reviews were carried out from 1997 to 2005 to identify ovarian cancer patients treated with neoadjuvant chemotherapy. Pathologic assessments of the extent of: tumour necrosis, fibrosis, macrophage infiltration, and tumour induced inflammation were graded on an ordinal scale of 0 to 2 (none/minimal, moderate, extensive). All pathology slides were reviewed and graded by one gynecologic pathologist. A composite pathologic tumour response score was calculated by summing all above pathologic assessments for each sample. Cox proportional hazard models were built to model time to clinical progression and death using predictor variables of: age, tumour grade, residual disease, and pathologic tumour response score. All p values less than 0.05 were considered to be statistically significant.

Results: Sixty-two patients with available slides for reviews were identified retrospectively. Optimal debulking was achieved in seventy four percent. Significant predictors for prolonged progression free survival included: younger age (p=0.05), optimal tumour residual status (p=0.016), and higher composite pathologic tumour response score (HR 0.848, 95% CI 0.742-0.970, p=0.0016). Cox regression modeling revealed only one significant predictive variable of time to disease related death being the composite pathologic tumour response score (HR 0.695, 95% CI= 0.515-0.938, p=0.017).

Conclusion: Pathologic assessments of tumour response to chemotherapy are helpful in determining prognosis and could be used to guide subsequent therapeutic decisions. The proposed composite pathologic tumour response score warrants further studies and validation.
OMENTAL CHEMOTHERAPY EFFECT AS A PROGNOSTIC FACTOR IN OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING

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Objectives: To assess the extent of chemotherapy effect on upper abdominal metastatic disease and its significance.

Methods: Retrospective chart reviews were carried out from 1997 to 2005 to identify ovarian cancer patients treated with neoadjuvant chemotherapy. Pathologic examination of resected omental and ovarian tumours for the presence of chemotherapy effect were performed by one gynecologic pathologist. Cox proportional hazard models were built to model time to progression and death using predictor variables of: age, tumour grade, amount, location of largest residual disease, and the presence of chemotherapy effect.

Results: Sixty-six patients with available slides for reviews were identified. Optimal debulking was achieved in fifty-five percent of patients. The presence of omental chemotherapy effect was observed in 58 patients (88%). Identified independent significant predictors for progression free survival included: presence of omental chemotherapy effect (HR 0.38 95% CI 0.17-0.89 p=0.026) and tumour residuals in upper abdominal locations compared to pelvic location (HR 2.41 95% CI 1.06-5.48 p=0.035). The presence of omental chemotherapy effect was the only significant positive predictor of disease specific survival (HR 0.21 95% CI=0.068-0.639 p=0.006). The estimated median survival for the group with positive omental chemotherapy response was 84.45 months (95% CI 69.63-99.28). The corresponding statistic in patients with no observed response to chemotherapy was 31.15 months (95% CI 21.84-40.47).

Conclusion: Upper abdominal disease location and its response to chemotherapy are independent prognostic factors for progression free survivals. Aggressive upper abdominal debulking procedures are indicated to improve oncologic outcomes.
CORONAL SERIAL SECTIONING OF LUMPECTOMY SPECIMENS
PROPOSED TECHNIQUE OF SECTIONING AND SUBMISSION OF TISSUE FOR MICROSCOPIC EXAMINATION OF BREAST CARCINOMA

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Background: Lumpectomy specimens are currently sectioned in a plane perpendicular to the long axis of the sample and skin (random serial sectioning technique -RSS). It is often necessary to correlate areas of tumor with radiological findings, which is often difficult with the RSS technique. We hypothesized that coronal sectioning has better reproducibility and might be a better alternative.

Design: Fifty lumpectomy specimens for breast carcinoma were sectioned in the coronal plane (parallel to the skin/chest wall) at 3-5 mm intervals (coronal serial sectioning technique - CSS). All giant sections of the breast tissue between the superficial and deep margins were divided in a “grid” pattern into routine sections. The superficial and deep margins were cut in the plane perpendicular to the coronal plane. For large specimens, the findings of this protocol were compared with two modified protocols involving fewer sections: Modified protocol 1) for cases with diffuse fibrosis or cystic changes (10 cases), findings on microscopic examination were recorded from entire alternate “giant” cross sections; Modified protocol 2) for cases consisting predominantly of adipose tissue (3 cases), findings of microscopic examination were recorded from fibrotic areas. Additional sections were required for areas suspicious for margins involved by carcinoma.

Result: CSS demonstrated DCIS and invasive carcinoma in its largest area and along the greatest diameter as opposed to the RSS that divided the greatest diameter of the breast lesion in multiple sections. Findings on status of DCIS, resection margins and multi-centricity, and dimensions of DCIS and invasive carcinoma were similar in three protocols of CSS for large specimens. But CSS had the following benefits over RSS: a) easily reproducible panoramic view of different areas and types of neoplasms in the sample, b) accurate measurement of tumor size, c) feasibility for reconstruction of the breast specimen to re-examine areas of interest after the initial microscopic examination, and d) no requirement of special equipment, extra-time of fixation or time-consuming training to achieve better results in comparison with conventional RSS.

Conclusion: We propose that CSS is more scientific and a better approach for processing lumpectomy samples of the breast.
Background: Bronchoalveolar carcinoma (BAC) is considered to be an in situ lesion, and surgical resection is assumed to be curative. It presents as a space occupying lesion in the lungs, appearing as a ground glass opacity which is then biopsied for cytological evaluation. Demonstration of a well-differentiated, localized tumor with lepidic growth pattern suggests a BAC. But well differentiated adenocarcinoma or an adenocarcinoma of mixed subtype with invasive patterns can also give a similar deceiving picture. The rate of concordance of radiologic and cytologic appearance of BAC with the subsequent final histological diagnosis is not well established.

Design: We did a retrospective search of all cases that were diagnosed as 'BAC' following FNAC at the Ottawa Hospital ('00 -'09). All cases had a prior CT scan and needed to have a subsequent wedge resection or lobectomy with evaluations done at our institution. Correlations between radiologic, cytological and subsequent histopathological diagnosis was then evaluated.

Result: 71 cases diagnosed as BAC by FNAC were found that had a prior CT scan and a subsequent surgical resection. Among these only 23 (32%) cases had a distinct ground glass opacity on CT scan. 8 (35%) of these were subsequently confirmed as BAC. 44(62%) cases did not have the radiologic appearance of BAC, but 11 (25%) of these were subsequently found to be BAC. Altogether only 28 cases (37%) were confirmed as BAC, 26 (36%) were invasive adenocarcinoma, 14 (19%) had a mixed subtype of both BAC and adenocarcinoma, and the remaining (5%) had multiple other malignant diagnoses.

Conclusion: The study shows that only 35% of lesions appearing as BAC on CT scan are subsequently confirmed by both cytology and histology. A cytologic diagnosis of BAC is inaccurate in >60% of cases. Such misdiagnosis of an invasive adenocarcinoma as BAC may give a wrong sense of relief to the clinician and patient, and even delay treatment. Since BAC is mostly a diagnosis of exclusion that cannot be made without histologic evaluation, we propose that, ‘BAC’ diagnosis should not be made by ‘radiology’ or ‘cytology’ alone, but rather needs a combined clinical, radiological and histo-pathological evaluation. Further studies are required to identify reasons for the discrepancy between radiological, cytological and histopathological diagnosis of BAC.
LEFT VENTRICULAR MESENCHYMAL HAMARTOMA: A NOVEL PRIMARY TUMOUR OF THE HEART

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Primary neoplasms of the heart are rare. Benign entities previously described in adult populations include myxoma (1), fibroma (2,3), lipoma (4), hamartoma of mature myocytes (5,6), and vascular hamartoma (7-10). The most common pediatric cardiac neoplasm is the rhabdomyoma (11). We report a 22 year old female with a primary cardiac tumour in the left ventricle which had elements of multiple mature mesenchymal tissues, including mature cardiac myocytes, smooth muscle, fibroblasts, mature fat, blood vessels including a hemangioma like area, as well as nerve fibers. The various elements were disorganized but well differentiated and showed little mitotic activity; features suggestive of a hamartoma. Unlike a cardiac fibroma, which may entrap myocardium at the periphery of the lesion, the present case demonstrated all tissue elements throughout the tumour mass. We suggest that this lesion is sufficiently different from those hamartomas previously described in the literature to warrant a new designation, for which we propose the title mesenchymal hamartoma.
DIFFUSE PULMONARY ALVEOLAR HEMORRHAGE IN MYELODYSPLASTIC SYNDROME

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Background: Diffuse alveolar hemorrhage (DAH) is a rare and frequently fatal condition characterized by widespread alveolar hemorrhage. The aetiologies are diverse and include vasculitides, connective tissue disorders, drugs, infections, diffuse alveolar damage and malignancies. Associated haematological neoplasms include leukemias and multiple myeloma. DAH as a manifestation of myelodysplastic syndrome (MDS) is a rare finding.

Design: A 79-year-old male with coronary artery disease and type II diabetes mellitus presented with petechiae. He had a history of viral-like symptoms three weeks previous to presentation. He was severely thrombocytopenic (platelets 4 x 10⁹/L) and immune thrombocytopenic purpura (ITP) was initially diagnosed. However, he was refractory to treatment with immunoglobulin, corticosteroids and cyclokapron. Hemoptysis developed and persisted, requiring multiple transfusions. While in hospital, the patient had a non-ST segment elevation myocardial infarction, acute renal failure, leukocytosis (24.0 x 10⁹/L) and fever, leading to broad spectrum antibiotic treatment. Cultures and rheumatologic work-up were negative. A bone marrow biopsy revealed MDS with multilineage dysplasia and excess blasts. His pulmonary hemorrhage precipitated hypoxic respiratory failure and cardiac arrest.

Results: At autopsy, petechiae were documented. Bilateral massive pulmonary hemorrhage was evident with right and left lungs weighing 1460g and 1640g respectively. Microscopically, there was extensive intra-alveolar hemorrhage with early diffuse alveolar damage, without evidence of vasculitis. Bacterial and fungal stains were negative. Severe dysplasia of the erythroid and megakaryocytic lineages was confirmed. The heart had a recent transmural and circumferential myocardial infarction involving the left ventricle.

Conclusions: Pulmonary hemorrhage is a rare and fatal complication in patients with MDS. Our case is novel in documenting fatal DAH as an initial presenting symptom of MDS.
STAPHYLOCOCCUS LUGDUNENSIS PREVALENCE IN A PAEDIATRIC MICROBIOLOGY LABORATORY.

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2Children’s Hospital of Eastern Ontario, Bacteriology Laboratory

OBJECTIVES: Staphylococcus lugdunensis (SL) has recently been reported to be a common cause of skin and soft-tissue infections (SSTI) that may be under-recognized with standard SSTI specimen protocols. SL is also known to cause serious infections such as acute endocarditis. However, SL infections have been predominantly reported in adult patients. To see if SL is clinically important in a paediatric population, we prospectively and retrospectively studied SL prevalence.

METHODS: Over 5 months, we prospectively screened for SL in wound, respiratory, ear, urine, sterile sites, and blood specimens from paediatric patients. Retrospectively, we identified all non-speciated coagulase negative Staphylococcus (CoNS) from sterile site and blood for 12 months. We utilized a standard SL identification protocol using pyrolidonyl arylamidase (PYR) and ornithine decarboxylase testing, and also tested the isolates with the Vitek 2 gram-positive panel. Molecular testing was used for confirmation.

RESULTS: 200 CoNS were screened and 7 isolates from 6 patients were found for a total prevalence of 3.0%. Four isolates were from urine catheter specimens of babies less than 2 months of age, one of which lead to specific treatment. Two of isolates from a peritoneal dialysis exit site of the same patient one month apart were considered skin colonizers. The last isolate was from a bone sample that required specific treatment and may have been misidentified as Staphylococcus aureus based on rapid testing alone had it not been for the study screening and technologist education. Retrospectively, SL was not identified in any of the 96 archived non-speciated CoNS isolates tested or in 45 previously speciated isolates.

CONCLUSIONS: Compared with adult population, SL has a similar prevalence in paediatric non-sterile site samples yet was considered to be not clinically significant in 5 of 6 isolates. Furthermore, SL was rarely found in invasive infections in children (1 of 165). Routine testing to identify SL from non-sterile sites in paediatric patients does not appear to be warranted. However, given the known virulence of S. lugdunensis, we believe identification of this bacterium in paediatric sterile site specimens is prudent, despite its low prevalence.
Study Objective: To review the relationship between endometriosis and epithelial ovarian carcinoma.

Design: Case report and review of the literature. A search of the literature was performed using key word searching and citation snowballing to identify English language articles published in the last ten years on the subject of endometriosis and its association with epithelial ovarian carcinoma. Once the articles were identified, a thorough review was conducted. Results and conclusions were compiled and summarized.

Results: There appears to be a strong association between endometriosis and epithelial ovarian carcinoma, in particular the clear cell and endometrioid subtype.

Conclusion: Ovarian clear cell carcinoma and endometrioid adenocarcinoma may arise from endometriosis and malignant transformation of endometriosis can occur at any age including prior to menopause. Clinicians should consider routinely performing biopsies in all patients undergoing laparoscopy for endometriosis, as well as performing ovarian cystectomy or possibly oopherectomy in post-menopausal women with endometriomas.
CONCURRENT CHEMO RADIATION FOR THE TREATMENT OF PRIMARY VAGINAL CANCER

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Objective: To evaluate the role of concurrent chemo-radiotherapy in the curative treatment of primary vaginal cancer.

Methods: A retrospective chart review was performed on all primary vaginal cancer patients treated at the Ottawa Hospital Regional Cancer Centre with curative intent using concurrent chemotherapy and radiotherapy, between 1999 and 2004. Disease-free and overall survival rates were analyzed using the Kaplan-Meier method.

Results: Twelve patients were identified as being treated with curative intent using concurrent chemotherapy and radiation therapy. The median age at diagnosis was 56 years (range 34 – 69 years) and the median follow-up was 43 months (range 11 – 75 months). Ten (83%) were diagnosed with squamous cell carcinoma and 2 (17%) with adenocarcinoma. The distribution according to stage was as follows: 5 (42%) stage II, 5 (42%) stage III and 2 (16%) stage IVA. All patients received pelvic external beam radiotherapy concurrently with weekly intravenous cis-platinum chemotherapy followed by brachytherapy. The median dose of external beam radiotherapy was 4500cGy given in 25 fractions over 5 weeks. Ten patients received interstitial brachytherapy and 2 patients received intracavitary brachytherapy, with the median dose being 3000cGy. The weekly dose of the intravenous cis-platinum chemotherapy was 40mg/m2. At the time of analysis, 3 patients had developed a recurrence and all three patients had died. The 5-year overall survival, disease-specific survival and loco-regional control rates were 73%, 80%, and 92%, respectively. Although acute grade 1 and 2 toxicities were noted among many of the patients, grade 3 toxicity requiring hospitalization and/or surgery occurred in only 2 patients (17%). None of the patients had a life threatening or fatal toxicity.

Conclusions: Chemo-radiotherapy is highly effective for the treatment of primary vaginal cancer patients and has an acceptable toxicity profile.

Background:
- Primary vaginal cancer is relatively rare (<2% of gynecologic malignancies)
- Optimal treatment is controversial but often radiotherapy is the main treatment modality utilized with locoregional disease control being the biggest concern
- Both external beam radiation and brachytherapy (interstitial or intracavitary) are considered important components of curative treatment
- The role of chemotherapy is not well defined with just one recently published study clearly documenting its use

Purpose:
- To determine the efficacy of radiotherapy in combination with concurrent weekly cis-platinum chemotherapy in the curative treatment of primary vaginal cancer
- To compare this approach with a historical cohort of patients treated with curative intent without the use of chemotherapy

Methods:
- A retrospective review was performed of all primary vaginal cancer patients treated with curative intent using chemo-radiation (radiotherapy...
consisting of external beam plus a brachytherapy boost with the addition of concurrent chemotherapy) since 1999

- We compared these patients to our previously published data* on 18 primary vaginal cancer patients treated with curative intent from 1989-2001 using radiotherapy alone (external beam + brachytherapy) without the addition of chemotherapy

**Results:**

- 12 primary vaginal cancer patients treated with chemo-radiation from 1999-2004
  - Median age 56 years (range 34-69 years)
  - Median follow-up 43 months (11-75 months)

**Tumor characteristics**

<table>
<thead>
<tr>
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<th>Number</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>FIGO Stage</strong></td>
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</tr>
<tr>
<td>II</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>IVa</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Lymph Node Involvement</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>83%</td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>10</td>
<td>83%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2</td>
<td>17%</td>
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<tr>
<td><strong>Tumor Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4</td>
<td>43%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>4</td>
<td>43%</td>
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<tr>
<td>Grade 3</td>
<td>2</td>
<td>17%</td>
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<tr>
<td>Grade X</td>
<td>2</td>
<td>17%</td>
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</table>

**Treatment Details**

- External beam radiation
  - Median dose 4500cGy/25fr/5weeks
  - 4-field box arrangement with 18MV photons used most commonly
  - Primary tumor and pelvic lymph nodes encompassed
- Brachytherapy
  - 10 patients received interstitial implants (LDR brachytherapy)
  - 2 patients received intracavitary implants (HDR brachytherapy)
  - Median dose prescribed 3000cGy
- Chemotherapy
  - Weekly intravenous cis-platinum given during external beam radiation
  - Dose 40mg/m²
Progression Free Survival

Overall Survival

Recurrences
- 3 recurrences have occurred thus far
  - 1 locoregional relapse, 2 distant relapses
  - 1 stage II pt, 1 stage III pt, 1 stage IV patient
• 2 patients had lymph node involvement at diagnosis and 1 had grade 3 disease
• All recurrences occurred within 2 years of completing treatment

**Toxicities**

• Difficult to accurately assess retrospectively from charts
• However, 75% had at least moderate acute toxicity involving the bowels, bladder or skin/mucosa (based on descriptions given)
• No Grade 3 or 4 acute hematologic toxicity but 1 patient was switched from cis-platinum to 5-FU for the last week of chemotherapy due to an elevated creatinine
• 2 patients (17%) had late grade 3 toxicity requiring surgery and/or hospitalization
  o Both developed fistulae requiring surgery
• 4 patients (33%) significant vaginal scarring (but it was not necessarily symptomatic)
• No life-threatening or fatal toxicities were noted

**Chemoradiation patients compared to radiotherapy only (previously published*) patients**

<table>
<thead>
<tr>
<th></th>
<th>5-year local control</th>
<th>5-year progression-free survival</th>
<th>5-year Overall survival</th>
</tr>
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<tbody>
<tr>
<td>Chemoradiation</td>
<td>92%</td>
<td>75%</td>
<td>73%</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation only</td>
<td>70%</td>
<td>59%</td>
<td>54%</td>
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<tr>
<td>(n=18)</td>
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*Includes local and distant recurrences, *FIGO stage distribution: I= 5, II=10, III= 2, IV=1

**Discussion**

• Local control with chemoradiation is excellent and appears better than most other series looking at either radiotherapy alone or surgery alone
• Overall survival and progression-free survival also compare very favorably with the published literature
• The improvement in local control appears to be the biggest reason for the better overall outcomes noted and are similar to those achieved in the one previously published study assessing chemoradiation for the treatment of vaginal cancer
• The apparent magnitude of benefit noted by the addition of cis-platinum chemotherapy in our non-randomized comparison is very similar to that achieved by the addition of concurrent cis-platinum to radiation among cervix cancer patients
• The toxicity of chemoradiation appears acceptable
• Longer follow-up is still required to fully determine the role of chemoradiation in the treatment of vaginal cancer but the present findings are very promising

**Conclusions**

• Chemo-radiation is highly effective for the treatment of primary vaginal carcinoma and needs to be considered as a treatment option for patients being treated with curative intent
Our preliminary results suggest that this treatment approach is more effective than radiotherapy alone and has an acceptable toxicity profile.

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References


PROGNOSTIC SIGNIFICANCE OF POST OPERATIVE MORBIDITIES IN ADVANCED EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Objectives: To examine the prognostic significance of postoperative morbidities in ovarian cancer patients treated with neo-adjuvant chemotherapy and interval surgical debulking.

Methods: Retrospective chart reviews of all patients treated with neoadjuvant chemotherapy and interval debulking were performed from 1999 to 2002. Descriptive statistics were used to summarize the distributions of important clinical variables. Logistic regression was used to identify significant predictors of postoperative morbidities. Cox regression was used to model time to first clinical progression. Survivals were estimated using Kaplan-Meier method and compared with the log rank tests. All p values less than 0.05 were considered to be statistically significant.

Results: Fifty-eight patients were treated with neoadjuvant platinum/taxane combination chemotherapy. Major surgical complications were observed in four patients (6.8%). There was no perioperative death. The presence of concurrent medical co-morbidities was associated with the development of significant post-operative morbidities (P=.038). Cox regression showed any macroscopic residual disease (P=.04) and the presence of significant postoperative morbidities (O.R =4.7 95% CI 1.8-12.7 P=.002) to be significantly predictive of a shorter progression free interval.

Conclusion: Neoadjuvant chemotherapy followed by interval surgical debulking appeared to carry a low risk for postoperative morbidities. The adverse influence of significant postoperative morbidities on progression free survivals needs further study.
Abstract:
Leiomyomas represent the most common gynecological and uterine neoplasms affecting 20 - 30% of women over 35 years of age. However, extra uterine leiomyomas are rare and can present a diagnostic challenge. These benign tumors originate from smooth muscle cells and can arise from practically any site in the body, although genitourinary origin is most frequent. Uncommon sites include labia majora, ovary, urethra, and urinary bladder. Unusual patterns of growth include benign metastasizing leiomyoma, disseminated peritoneal leiomyomatosis, intravenous leiomyomatosis, parasitic leiomyomas and retroperitoneal growth. In these cases with rare growth patterns, a synchronous leiomyoma in the uterus or history of prior hysterectomy for removal of the primary tumor may or may not be present. Although histologically benign, these rare presentations may mimic malignant tumors with the potential for serious diagnostic errors. Imaging modalities include sonography, CT and MRI. Superb contrast resolution and multiplanar capabilities of MRI make it particularly valuable in characterizing these lesions. In the appropriate clinical setting, consideration of these tumors amongst the list of other differential diagnoses can help the radiologist guide the clinician to choose timely and appropriate management thereby avoiding unnecessary and sometimes potentially harmful treatment.
THE IMPORTANCE OF OPTIMAL INGUINAL FEMORAL NODAL DISSECTION IN THE MANAGEMENT OF VULVA SQUAMOUS CELL CARCINOMA

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Objectives:
To assess the prognostic significance of the number of inguinal lymph nodes removed at time of surgical staging for vulva carcinoma.

Methods:
Retrospective chart reviews were carried out from 1980 to 2004 to identify patients with squamous cell vulva carcinoma treated with radical vulvectomy and bilateral inguinal femoral lymph node dissection. Patients' demographics, disease characteristics, the number of lymph nodes removed at surgery and standard oncologic outcomes were recorded. Cox proportional hazard models were built to model times to clinical progression and death using predictor variables of: age, tumour size and maximum depth of invasion, resection margin status, and total number of nodes removed.

Results:
Fifty-eight patients were identified. The median lesion size was 3.5 cm. The median depth of invasion was 7.5 mm. The 20th centile for total number of lymph nodes removed was 10. Adjuvant radiation therapy was given in 31% of patients due to positive tumour margin or metastatic nodal disease. At a median follow up of 37 months, recurrence was observed in 17 patients (29.3%). Cox regressions showed the total number of nodes removed less than 10 to be the only significantly predictive of shorter time to first progression (HR = 12.88, 95% CI=1.47-112.89, p=0.021) and shorter disease specific survivals (HR= 11.41, 95% CI=2.21-58.86, p=0.004).

Conclusion:
The total number of nodes removed at time of surgical staging is an independent survival prognostic factor. An average of five nodes from each side can be used to define an optimal dissection.
SIGNIFICANCE OF CA125 RESPONSE IN EPITHELIAL OVARIAN CANCER PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGICAL DEBULKING

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Objectives:
To examine the prognostic significance of Ca125 response to neoadjuvant chemotherapy and delayed primary surgical debulking in ovarian cancer patients.

Methods: Retrospective chart reviews were carried out from 1997 to 2005 to identify ovarian cancer patients treated with neoadjuvant chemotherapy. Ca125 response was defined as being a decrease of at least 50% from baseline assessment. Ca125 response was assessed at two time points: prior to surgical debulking to reflect the response to neoadjuvant chemotherapy and at the end of primary chemotherapy to assess the response to debulking surgery and further chemotherapy. Cox proportional hazard models were built to model progression free intervals using predictor variables of: age, cancer stage, tumour grade, residual disease, and Ca125 response.

Results: Ninety-one patients were identified. Eighty three percent had a positive Ca125 response following 3 cycles of neoadjuvant chemotherapy preoperatively. Cox regressions revealed two significant predictive variables of prolonged time to first progression: younger age (p=0.002) and microscopic residual disease compared to suboptimal disease (p=0.003). Ca125 response to neoadjuvant chemotherapy was not significantly associated with progression free survivals. The estimated mean survival was 71.42 months (95% CI 44.34- 78.50) in patients with >50% Ca125 decrease from surgery and further chemo whereas in those with no response, the corresponding survival estimate was 44.02 months (95% CI 33.26-54.79).

Conclusion: The lack of Ca125 response from neoadjuvant chemotherapy is not an independent prognostic factor. All patients treated with neoadjuvant chemotherapy should undergo radical debulking surgery.