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Title: Spindle-cell alteration of endometrial stroma as a predictor of plasma cell infiltration.

Authors: Bollin-Richards B, Siddiqui M, Lieberman R and Habib L

Background: Chronic endometritis is an inflammatory condition of the endometrium that is histologically characterized by the presence of plasma cells. Identification of plasma cells, however, can be difficult secondary to a variety of factors including low numbers, presence of mononuclear cells, and plasmacytoid-stromal cells. The routine use of immunohistochemical staining is not cost-effective, and detailed high-powered examination is a time-consuming process. This study investigates the phenomenon of spindle-cell alteration of endometrial stroma, which has been noted in chronic endometritis. We aim to determine if spindle-cell alteration can serve as a surrogate marker for the presence of plasma cells. We also compare the treatments and outcomes for the patients present in this study.

Methods: Specimens from endometrial biopsies and curettings were examined prospectively with standard H&E sections from 372 patients. When taken through two rounds of exclusions, the final group contained true spindled stroma and true non-spindled stroma. This group of specimens was then assessed for presence of plasma cells using CD 138 immunohistochemistry (IPOX). Patient data from the final group was then retrospectively reviewed and statistically analyzed for differences in their characteristics, treatments, and outcomes.

Results: The final cohort consisted of 61 patients, 43 of which contained spindled stroma and 18 that contained non-spindled stroma. Forty-one of the spindled specimens contained plasma cells, and in the non-spindled group, 11 contained plasma cells. The odds ratio of having plasma cells in spindled stroma is 13.045 ($p = 0.002$). There is a greater likelihood of being in proliferative phase in both spindled stroma and in stroma with plasma cells ($p = <0.001$ and 0.012, respectively). Spindling as a marker of plasma cells has a 79% sensitivity and a 78% specificity with a 95% PPV and a 39% NPV, respectively. Results from the analysis of other patient characteristics are pending.

Conclusions: Although there is a significant association of spindle-cell alteration of endometrial stroma with plasma cell infiltration, using this finding as a marker for the presence of plasma cells has a high false negative rate, and therefore a poor NPV. Conclusions from the analysis of other patient characteristics are pending.

Title: Evaluation of the HGF/Met receptor tyrosine kinase pathway in epithelial ovarian cancer.

Authors: Bowes R, Liu RJ, Gossner G and Lieberman R

Objective: Hepatocyte growth factor/scatter factor (HGF/SF) and its tyrosine kinase receptor, c-Met, have been associated with many tumor types, and expression correlates with metastatic disease and overall poor prognosis. HGF/SF-Met can modulate cell proliferation, invasion, and angiogenesis in cancer cells. The purpose of our study was to elucidate the relationship between the expression of phosphorylated (activated) c-Met, along with proteins important in the regulation of angiogenesis, and prognosis in epithelial ovarian cancer patients.

Methods: Archival tumor specimens (paraffin blocks) from epithelial ovarian cancer patients who underwent staging surgery at the University of Michigan between the years of 1990-2000 were collected. A tissue microarray was constructed as follows: H&E slides were marked to indicate the area of core sampling of paraffin tumor specimens. 103 tissue core samples one millimeter in diameter were placed on a glass slide in a grid formation and immunohistochemical stainings of phosphorylated c-Met, vascular endothelial growth factor (VEGF), were performed. Benign control specimen samples were also included on the microarray grid. A matching clinical database containing demographic information, date of diagnosis, date of surgery, history of chemotherapeutic regimens, date of recurrence, and overall survival has also been created and data analysis is ongoing.

Result(s): Preliminary qualitative and quantitative staining analyses of c-MET and VEGF was performed in 88 tumor specimens collected from 39 patients. Staining for c-Met was almost uniformly 4+ and strongly intense. Differential staining patterns including nuclear, membranous and cytoplasmic variants were observed. VEGF staining was uniformly diffusely cytoplasmic, however differences were noted both in intensity of staining and in the proportion of cells expressing VEGF in the tumor specimens examined.

Conclusions: Our preliminary results indicate that c-MET is overexpressed in the majority of epithelial ovarian cancers. The differential staining patterns seen for c-MET seem to correlate with specific histologic subtype of the tumors rather than stage of disease. VEGF expression patterns and intensity were varied and further analysis, including collection of clinicopathologic parameters is ongoing to elucidate the relationship of tumor stage and prognosis to the c-MET pathway. We hope to determine if expression of these proteins are significant predictors of prognosis in epithelial ovarian cancer patients.

Title: Steroidogenesis Acute Regulatory Protein and Cholesterol side-chain cleavage enzyme.
Authors: Brahma P, Peegel H, Nair A, Fisseha S and Menon KMJ

Objective: The goal of the present study was to examine whether there is abnormal expression of key ovarian steroidogenic enzymes in women with polycystic ovarian syndrome (PCOS), by measuring the levels of mRNA using Real-Time PCR in women undergoing in vitro fertilization. Specifically, we determined the mRNA levels of cholesterol side-chain cleavage enzyme (CYP11A), 17 α -hydroxylase lyase (CYP17), and Steroidogenesis Acute Regulatory Protein (StAR). These enzymes play a role in translocation of cholesterol and its conversion to androgens and other steroids. Since insulin has been shown to up-regulate cholesterol transport into the ovary, we investigated whether hyperinsulinemia associated with PCOS results in the induction of molecules involved in sterol metabolism in the ovary.

Methods: Granulosa cells were isolated from the retrieval fluids after oocyte removal in fourteen patients who were undergoing IVF. Twelve women were ovulating normally and two women had polycystic ovarian syndrome. Granulosa cells were isolated by Ficoll density gradient centrifugation. Total RNA was extracted from the granulosa cells and the RNA was reverse transcribed. Real-Time PCR was performed to quantitate the levels of StAR, CYP11A, and CYP17 using specific primers. The expression of the three mRNAs was calculated with 18S ribosomal RNA as an internal control.

Results: This study showed differences in mRNA expression of both StAR and CYP 11A in PCOS women compared to normally ovulating women. CYP17 expression showed no difference between normal and PCOS ovaries. The mean quantity of mRNA expression of StAR in PCOS women was six times greater compared to normal ovulating women (74.8 ng \pm 5.5 vs. 11.6 ng \pm 3.3, respectively). In addition, the expression of CYP11A in PCOS women was fifteen times greater than in normal ovulating women (66.8 ng \pm 2.2 vs. 4.4 ng \pm 0.9, respectively).

Conclusions: The endocrine abnormalities associated with PCOS may play a role in hyperstimulating the expression of CYP11A and StAR in granulosa cells. Steroidogenesis in the gonads requires the translocation of cholesterol from the outer to the inner mitochondrial membranes and this process is mediated by steroidogenic acute regulatory (StAR) protein. CYP11A further converts intramitochondrial cholesterol to pregnenolone which is then further converted to other steroids including androgens. The induction of these two enzymes in PCOS ovaries suggests that elevated levels of these enzymes might contribute to the hyperandrogenism associated with PCOS.

TITLE: Perception and Use of Complementary and Alternative Medicine (CAM) Among Obstetrics/Gynecology Patients at the University of Michigan.

AUTHORS: Furlow M, Rhode J, Patel D, Sen A, Johnston C and Liu RJ

Objective: Complementary and Alternative Medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine as a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine. In 1993, 34% of adults in the United States had used at least one complementary therapy during the past year. A follow-up study in 1997 indicated that the use of CAM had increased to 42% of the general population. CAM use was found to be most common among reproductive age, educated, employed women. In this study, we sought to determine the general attitude and use of CAM among general obstetrics and gynecology patients at the University of Michigan.

Methods: Surveys were given to a sample of 500 women who visited an obstetrician gynecologist at the University of Michigan Taubman Center Clinic in May of 2005 and voluntarily agreed to complete the questionnaire. Patients were asked to rate their perception of effectiveness and to record their approach to specific CAM modalities. In addition, general attitudes toward CAM were polled. Descriptive analyses were conducted using T-tests, correlation tests, and multiple regression models. All data analyses were performed using SAS version 9.1.

Results: Overall, 65.9 % of patients reported use of at least one type of CAM. The top 5 most commonly used therapies were Exercise (36.3%), Vitamins/supplements (28.8%), Prayer (26.7%), Massage (19.0%) and Yoga (14.0%). When looking specifically at the most commonly used vitamins and herbs, 51% of patients using vitamins did so for pregnancy related symptoms. The most commonly used herb was evening primrose (13.1% of patients), and of these patients, 99% used evening primrose for menstrual or menopausal symptoms. The majority of patients using CAM (63.3%) did not consult with a health care provider prior to starting the alternative therapy. The most commonly cited reason (43%) was that their health care provider never asked about their use of other therapies. However, of the 29.2% people who did consult their healthcare provider before starting CAM therapy the majority (57.9%) said that their doctors encouraged them to continue using CAM.

Conclusions: Our preliminary data suggests that CAM use is prevalent among our obstetric and gynecologic patients at the University of Michigan. In addition, most patients using CAM did not consult a healthcare provider prior to starting therapy simply because their provider did not ask. This could lead to significant risks to the patient including delay in seeking appropriate conventional treatment, incorrect diagnosis, interference with the mechanism of action of a prescribed medication, or harmful reactions from ingested substances. Therefore, it is important for physicians to inquire and counsel their patients about their use of CAM and to provide information regarding safety and effectiveness.

Title: Gynecologic primitive neuroectodermal tumors are characterized by MIC-2 expression and the absence of common EWS-ETS translocations.

Authors: Hajra K and Cho KR

Objectives: Primitive neuroectodermal tumors (PNETs) uncommonly arise in gynecologic primary sites and represent a diagnostic and therapeutic challenge. Further understanding of the immunophenotype and genomic translocations of gynecologic PNETs may facilitate accurate tumor diagnosis.

Methods: Six gynecologic PNET cases were identified through our institution, four uterine, one cervical, and one arising in the round ligament. Immunohistochemical staining was done for MIC-2, vimentin, S-100, neuron-specific enolase, chromogranin A, synaptophysin, desmin, and PGP 9.5. For analysis of EWS-ETS translocations characteristic of PNETs, RNA was extracted from formalin-fixed, paraffin-embedded tumor specimens. cDNA synthesis and PCR amplification were performed with standard methods, using PCR primers detecting approximately 85% of EWS-FLI1 and EWS-ERG fusion transcripts.

Result(s): MIC-2 was expressed in all cases. Five cases had membranous MIC-2 staining and expressed neuron-specific enolase. One uterine case had punctate, cytoplasmic MIC-2 staining and failed to express neuron-specific enolase. All cases were negative for synaptophysin and chromogranin A. Variable staining was observed for the remaining proteins. For translocation analysis, RNA extraction was successful from five of six specimens, yet RT-PCR failed to demonstrate the presence of common EWS-FLI1 and EWS-ERG translocations.

Conclusion(s): The tumors diagnosed at our institution as gynecologic PNETs uniformly expressed MIC-2. However, the absence of commonly reported translocations in the tumors analyzed suggests that gynecologic PNETs may harbor novel EWS-ETS translocations. Alternatively, given the lack of genetic findings consistent with the diagnosis of PNET, perhaps a broader diagnostic spectrum should be entertained in evaluating the MIC-2-positive gynecologic small blue cell tumor.

Title: Changes in Medical Student Attitudes Regarding the Need for Informed Consent during Clinical Clerkships.

Authors: McCarthy J, Hammoud M, Katz N and Dugoff L

Objective: The purpose of our study was to determine whether any third year clinical clerkships impacted medical student attitudes regarding the need to obtain informed consent from patients.

Methods: Third year medical students from 3 medical schools across the country were recruited to complete a questionnaire before and after their obstetrics and gynecology (Ob/Gyn) clerkship exploring their opinions regarding the need to obtain informed consent from a patient in a variety of situations. They were asked to rate the importance of obtaining the consent on a scale of 1 (very unimportant) to 5 (very important). Using paired T-test, we examined the impact of the obstetrics and gynecology clerkship on students' perceptions of the need for informed consent. Using independent T-test, we examined whether completion of any other clerkship(s) had influenced student attitudes towards the need for informed consent. Gender differences were also examined.

Result(s): Six hundred surveys were completed, with 268 students completing both the pre- and post-clerkship surveys. After completion of the Ob/Gyn clerkship, students' attitudes towards the need to obtain informed consent from patients decreased significantly in 6 out of the 9 situations asked with $p < 0.05$. These were taking blood pressure, examining the abdomen, performing a pelvic or rectal in office, suturing at end of surgery, performing a rectal exam under anesthesia, and performing a pelvic exam under anesthesia. The three situations which did not significantly change were holding retractor during surgery, watching a surgery, and intubating a patient in the operating room. In the pre-clerkship survey, students who had completed the surgery clerkship versus those who did not had rated the importance of obtaining informed consent lower in all areas above ($p < 0.05$) except for watching a surgery and holding a retractor during surgery. In addition, differences were detected in 5 out of the 9 above areas for students who completed the psychiatry clerkship versus those who did not. No such differences were found among students who completed other clerkships including internal medicine, family practice, pediatrics or neurology. Women felt it was more important to get informed consent than men in all the situations and these differences were larger after the completion of the Ob/Gyn clerkship.

Conclusion(s): The obstetrics and gynecology clerkship, the surgery clerkship and the psychiatry clerkship appear to negatively impact students' attitudes regarding the need to obtain informed consent from patients. Furthermore, male medical students feel it is less important to obtain consent than female medical students. These findings come despite the press around the informed consent for pelvic exams under anesthesia and highlight the importance of more formal student education on the importance of informed consent during their clinical clerkships.

Title: Hyaluronic Acid: Effects on Mouse Embryo Development in Microfluid Environments.
Authors: Montville C, Silva C and Smith GD

Background: Glycosaminoglycans (GAG) are known to play an integral role in cell-to-cell interaction and differentiation of a variety of epithelial cell types. Hyaluronic Acid (HA) is a GAG found throughout the mammalian reproductive tract. Recent evidence has demonstrated that soluble HA significantly enhanced development of porcine and bovine embryos when added to embryo culture media.

Methods: In the present work, the effects of both insoluble and soluble forms of HA on mouse embryo development were assessed in microfluid environments. One-cell mouse embryos were cultured in the presence and absence of an insoluble woven benzyl ester of hyaluronic acid, HYAFF™, in one-hundred twenty microliters (µl) of culture media (P1 +1% SSS).

Results: Neither embryo viability, nor twelve hour incremental development rate, were significantly enhanced compared to controls. One-cell embryos were also cultured in agarose wells containing either 0.1% mucin (a glycosaminoglycan) or 0.3M soluble HA with five µl culture media (KSOM). No improvements in embryo viability or twelve hour incremental development were noted when compared to controls. Furthermore, in many of the experimental culture groups (mucin and HA), embryo growth was compromised compared to controls.

Conclusions: Growth of one-cell mouse embryos in microfluid environments may necessitate greater attention to the presence or absence of growth factors and waste by-products. In preliminary studies evaluating the role of GAGs in mouse embryo development in small culture media volumes, Hyaluronic Acid may deter, rather than enhance, embryo development in culture.

Title: The Effect of Gender and Video Game Experience on Medical Students' Performance in Virtual Reality Laparoscopy.

Authors: Saunders N, Hammoud M, Andreatta P and White C

Purpose: To evaluate whether prior video game experience, in conjunction with gender, impacted third-year medical student performance of basic laparoscopic skills on a surgical laparoscopic simulator.

Methods: As part of a clinical skills foundation curriculum, 148 third-year medical students spent 15 minutes on a laparoscopic surgical simulator (LapSim™) performing seven different tasks associated with a module on basic laparoscopic skills. The LapSim™ recorded performance parameters on each task. Time to complete each task was used to detect differences in performance based on gender and previous video game experience as reported by the students.

Results: No significant differences in performance on any of the seven LapSim™ tasks were detected based on gender or previous video game experience. There were also no significant interaction effects between gender and video game experience on any of the tasks.

Conclusions: Students' performance on a virtual laparoscopic simulator is not affected by gender or prior history of video game experience.