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Salivary Estrogens Androgens and Aromatase Inhibitors by LC-MS/MS in Breast Cancer Patients Treated With Testosterone Pellets Combined With Aromatase Inhibitors

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Introduction: High dose testosterone (T) has been used for treating hormone-sensitive breast cancers for many years. However, a drawback to T therapy is its propensity to convert to estradiol (E2) via aromatase, which can override the growth inhibitory effects of T and stimulate estrogen sensitive tumors. Aromatase is higher in some women than others, particularly those with active tumors, truncal obesity, and inflammatory conditions contributing to and caused by cancer. Oral aromatase inhibitors (AI) have been used to prevent conversion of T to E2. While this effectively reduces E2 burden, systemic oral AI require higher dosing, which often leads to severe side effects. As an alternative to oral AI therapy, researchers have found that T combined with a much lower dose of AI in a solitary pellet implant placed in the subcutaneous (SC) tissue, or alternatively, into the breast adjacent to a primary tumor, is effective in reducing tumor burden and maintaining a low systemic level of E2, while reducing the adverse side effects of very low E2. **Study Design:** In this case study we report on the use of an LC-MS/MS method to monitor salivary levels of E2, Estrone (E1), T, and the AIs Letrozole (LET) and Anastrozole (ANZ) following T + AI therapy in a breast cancer patient (intolerant of oral LET) with active (measurable) tumor in the breast and metastatic disease. Steroids and AIs were measured in saliva at baseline, 1 week, and 4 weeks after insertion of subcutaneous pellets containing '60 mg T + 4 mg ANZ' and '60 mg T + 6 mg LET'. **Results:** LC-MS/MS (range values-pg/ml) for postmenopausal women, and baseline, week 1 and week 4 post treatment values for each steroid and AI were: E2: (range 0.3-0.9), 0.4, < 0.3, < 0.3; E1: (range 0.9-3.1), 1.0, <0.4, <0.4; T: (range 7-22), 6, 96, 48; ANZ: (range <4), < 4, 2063, 24; LET: (range <4), < 4, 744, 175. Self-reported (Pre/Post Therapy) estrogen deficiency symptoms such as hot flashes, night sweats, vaginal dryness, joint pain, and sleep disturbances were significantly improved post T+AI therapy. In addition, the intramammary tumor decreased in size > 95% by month 5. **Summary:** These results show that low-dose SC AI therapy (4-6 mg/2-3 months = 0.1 mg/day) with T (120 mg/2-3 months = 1-2 mg/day) increases T to supra-physiological levels, prevents T metabolism to estrogens E2 and E1, reduces estrogen deficiency symptoms, and has beneficial effects on tumor growth inhibition. Simultaneous testing of sex-steroids E2, E1, T, and aromatase inhibitors LET and ANZ by LC-MS/MS provides a convenient means to monitor the bioavailable levels of these analytes and adjust them as necessary to optimize therapeutic efficacy and reduce adverse side effects.

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The Story of a Radiologically Undetectable, Testosterone Producing Leydig Cell Tumor

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Introduction: Leydig stromal cell tumors are uncommon ovarian tumors that produce testosterone leading to hyperandrogenism. We present a case of a 63 year old lady with significantly elevated testosterone levels that did not have clear ovaries visualized on imaging, but was subsequently found to have a Leydig cell tumor on pathology after ovarian resection.

Clinical Case: A 63 year old female with a past medical history of COPD, hypothyroidism, hyperlipidemia, hypertension and uterine fibroids status post hysterectomy and left oophorectomy in 1995 was referred to endocrinology for hirsutism. The patient reported first noticing abnormal hair growth approximately one year prior to presentation having developed increasingly coarse and thick facial hair, abdominal wall hair, and chest hair. On physical examination, she was noted to have coarse hair across her upper lip and chin continuous along the jawline along with fine, dark hair diffusely across her anterior abdomen. Initial laboratory cell evaluation revealed total testosterone 378 ng/dL, free testosterone 53ng/dL, DHEAS 64 ug/dL. Repeat labs drawn three months later confirmed the markedly elevated total testosterone of 362 ng/dL and free testosterone 44.2 ng/dL, concentrations normally seen in males. A CT scan of the abdomen and pelvis was done and did not reveal any masses. In addition, no ovaries were appreciated on imaging. A transvaginal ultrasound also did not reveal any clear ovaries. The patient ended up undergoing a right oophorectomy. Histological examination was consistent with a Leydig cell tumor. Following oophorectomy, her testosterone concentrations normalized (5ng/dL) and hirsutism began to regress.

Clinical Lesson: Hyperandrogenism in women is typically classified into non-tumorous and tumorous. The differential for non-tumorous hyperandrogenism includes PCOS, congenital adrenal hyperplasia (CAH), and ovarian hyperthecosis. Tumorous causes include ovarian tumors such as Sertoli-Leydig cell tumors, hilus cell tumors, and theca cell tumors. Adrenal tumors secreting testosterone are extremely rare. Often with these tumors, there is significantly increased testosterone levels (> 140ng/dL) and rapid progression of symptoms. Sex cord stromal tumors account for only 5-8% of all ovarian tumors with Leydig stromal tumors a rare group that accounts for less than 0.1% of all ovarian tumors. The tumors are functional producing testosterone leading to marked hyperandrogenism and virilization. They are also usually benign and unilateral. This patient had hyperandrogenism manifested by hirsutism with markedly elevated testosterone concentrations.

In addition, this case is unique in that a CT scan and transvaginal ultrasound did not clearly demonstrate her right ovary. Despite having a normal appearing right ovary during surgery, patient was found to have Leydig cell tumor following histological examination.

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Think Outside the Thorax: Doege-Potter Syndrome Presenting as a Retroperitoneal Mass

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Introduction: Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome, occurring less commonly than insulinoma. These tumors produce high molecular weight insulin-like growth factor-2 or "big IGF-2", resulting in hypoglycemia: big IGF-2 decreases glycogenolysis, gluconeogenesis, and glucagon release as well as increases glucose uptake by adipocytes and skeletal muscle. NICTH specifically associated with a solitary fibrous tumor (SFT) is known as Doege-Potter syndrome. Doege-Potter syndrome is seen most with thoracic SFT's. This case study details the diagnosis and management of Doege-Potter syndrome due to retroperitoneal SFT.
Case Description: Our patient is a 68-year-old, white female who initially presented to an outside facility with a 3-week history of episodic neuroglycopenic symptoms temporarily relieved with eating. She reported night sweats but no weight change or fever. Medical history was notable only for hypertension and GERD. She had no personal or family history of diabetes. She was transferred to our facility for further evaluation of an 18.6 cm multilobular mass seen just inferior to the liver on abdominal CT. Whipple's triad was confirmed with venous glucose sampling while inpatient. C-peptide, free/total insulin, and proinsulin were collected during permissive hypoglycemia and were low. Morning cortisol and TSH were unremarkable. Additionally, sulfonylurea screen and insulin antibodies were negative. Ultrasound-guided biopsy of the lesion was positive for CD34 and STAT6, consistent with SFT. Refractory hypoglycemia was treated with D5W infusion until surgical resection of the retroperitoneal mass, after which, she had complete resolution of her hypoglycemia.
Discussion: This patient's serum IGF-2 was within normal limits, consistent with reports of feedback inhibition exerted by increased levels of big-IGF-2. Therefore, the IGF-2:IGF-1 ratio is used to determine increased serum levels of big IGF-2, but this test is not widely available. SFT's can recur within months to years of resection, necessitating surveillance. Recurrence is also more common with extrathoracic tumors. Surgical pathology noted tumor dimensions of 22 cm and 2270 g; mitotic rate was 1 per 10 hpf. Features typical of malignancy include large size (>15 cm) and mitotic rate >4 mitoses per hpf. This patient's follow-up CT abdomen at 6 weeks did not show any findings to suggest recurrent or metastatic disease.

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Tissue Is the Issue - A Case of Malignant Insulinoma

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Introduction: Insulinomas are rare, functioning pancreatic neuroendocrine tumors, predominantly benign (90%). Most are sporadic, but they can occur as part of inherited disorders. Large size insulinomas are more likely to be malignant. ^{68}Gallium (Ga)-DOTATATE scan is an essential tool in diagnosis and treatment of pancreatic neuroendocrine tumors. However, tissue diagnosis is the ultimate prognosis predictor and treatment guide.
Clinical Case: An 80-year-old man presented with left ankle fracture after a syncopal episode. In the past several months he reported multiple episodes of lightheadedness. He denied history of diabetes. Past medical and surgical history included prostate cancer, gastroesophageal reflux disease and bilateral orchiectomy for undescended testes. His left ankle appeared swollen, otherwise the exam was unremarkable: he was well-nourished, the abdomen was soft and nontender, there were no palpable masses. He was noted to have several episodes of hypoglycemia. Hypoglycemia work up included negative sulfonylurea screen, plasma glucose 51 mg/dl (60-99 mg/dl), insulin of 31 uIU/ml (3-25 uIU/ml), proinsulin 85.4 pmol/L (<8 pmol/L), C peptide 3.4 ng/ml (1.1-4.4 ng/ml). Abdominal Computed Tomography with contrast showed a 4.7 x 3.1 cm exophytic mass in the body of pancreas, a 5.3 x 5 cm mass in the head of pancreas and multiple ill-defined hepatic lesions concerning for metastatic disease. ^{68}Ga-DOTATATE scan revealed an avid pancreatic mass and multiple avid foci throughout the liver suspicious for metastatic disease. Octreotide and intravenous dextrose were started for the treatment of persistent hypoglycemia. He underwent Whipple procedure and resection of the metastatic liver lesions. Postoperatively hypoglycemia resolved. The pathology revealed large cell pancreatic neuroendocrine carcinoma with areas of well differentiated tumor and multiple liver metastatic neuroendocrine carcinoma, Ki-67 of 50-80% was reported in the primary tumor and metastatic lesions.
Discussion: Metastatic insulinomas carry a significant morbidity and mortality risk. Surgical resection to decrease tumor burden can reduce the risk of hypoglycemia. Histopathology is essential in treatment decision making. Surprisingly our patient's pathology revealed poorly differentiated neuroendocrine carcinoma, changing the prognosis and treatment. Treatment with platinum-based chemotherapy and etoposide is the standard of care for aggressive neuroendocrine neoplasms. Despite hypoglycemia resolution following surgery and good DOTATATE uptake by the well differentiated neuroendocrine tumor portion, our patient's prognosis remained poor in view of the high-grade carcinoma. Due to complicated hospital course, and decreased functional status patient was not a candidate for chemotherapy immediately post hospital discharge.