mechanism is not fully understood. In vitro and in vivo animal studies have shown elevated T3 activity can induce hepatocyte apoptosis via a mitochondrial-mediated pathway. This case demonstrates a patient with elevated aminotransferases and hepatic apoptosis most likely secondary to severe hyperthyroidism.
Clinical Case:
50 year old female with a past medical history of migraines was seen by primary care for fatigue and 15 lb weight loss in one month. She was found to be hyperthyroid with TSH < 0.1 uIU/L (n=0.34-5.6), free T4 3.48 ng/dL (n=0.58-1.64) and mildly elevated aminotransferases of AST 77 IU/L (n=15-41), ALT 144 IU/L (n=12-63), which increased within a week to 159 IU/L and 309 IU/L respectively. ALP and bilirubin were within normal range. She was started on methimazole 20 mg twice daily by her PCP. The patient developed vomiting and stopped taking methimazole after 3-4 days. Upon initial presentation to endocrine clinic, found to be clinically hyperthyroid and as LFTs were improved but still elevated, she was re-challenged with methimazole at a lower dose as well as started on a beta blocker and cholestyramine. TT3 checked was elevated at 2.10 ng/mL (n 0.87-1.78). Graves' disease was confirmed with elevated TSI as well as RAI uptake and scan showing increased homogenous uptake.
She had extensive workup for another etiology by hepatology including autoimmune, which were negative. Her fibrosis score was stage F1-F2 (n=F0) and necroinflammatory activity grade A3 indicating severe activity (n=grade A0). Core needle biopsy of the liver showed focal lytic necrosis/apoptosis and abundant pigment-laden Kupffer cells signifying recent hepatocellular injury. Her AST and ALT down trended and normalized with repeat fibrosis score of F1 and necroinflammatory activity grade A0. She eventually had definitive therapy with RAI treatment.
Conclusion: In most cases of hyperthyroid induced liver dysfunction, liver histology showed fatty infiltration, cytoplasmic vacuolization, nuclear irregularity and hyperchromatism.
This case, without any other known causes that could explain her hepatic injury, indicates the possible role of hyperthyroidism in hepatic apoptosis.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Prostatic Acid Phosphatase Is Not Regulated by Androgens During Prostate Development and Tumorigenesis

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SUN-143

INTRODUCTION: Prostatic acid phosphatase (PAP) is a soluble factor secreted by prostate luminal epithelial cells. PAP expression correlates with prostate cancer (PCa) bone metastases and poor survival. The androgenic regulation of PAP in prostate development and tumorigenesis is not fully understood. We investigated the relationship between PAP and androgens in human prostate specimens and *in vivo*. HYPOTHESIS AND OBJECTIVES: We hypothesized that PAP expression was independent of androgens. Our objectives were to determine the immunohistochemical expression of PAP in human fetal prostate tissue, human PCa bone metastases, and xenograft and surgical castration mouse models. METHODS: Immunohistochemical staining for PAP and three androgen-regulated proteins, the Androgen Receptor (AR), Prostate-Specific Antigen (PSA), and ETS-related gene (ERG) protein, was carried out on human fetal prostate (9.5, 11.5, 13, 16.5, 18 and 20 weeks of gestational age), archival human PCa bone metastases, and PCa mouse models. For xenograft studies, PAP-expressing PCa cell lines, LNCaP, C42B, and VCaP cells, were inoculated subcutaneously into SCID mice. A castration study with surgical or sham castration was performed after VCaP tumors were palpable. Mouse tumor growth and weight were measured biweekly, and tumor tissue isolated after mouse sacrifice. RESULTS: PAP expression was observed in the fetal prostate as early as 11.5 weeks of gestational age. Strong PAP expression was noted in all human PCa bone metastases examined, both treatment-naive and castrate-resistant (n=10). However, AR and ERG expression was absent in two of four castrate-resistant specimens. PSA was weakly expressed in human castration-resistant bone metastatic prostate specimens. *In vivo*, PAP expression was observed in all tumor models; however, the expression of PAP differed among androgen-sensitive models; LNCaP (low PAP), C42B (moderate PAP) and VCaP (high PAP). Castrated VCaP tumors underwent tumor stasis and were significantly smaller compared to intact mice. Strong expression of PAP was observed after castration. In contrast, AR, PSA, and ERG expression were reduced in castrated VCaP tumors compared to tumors from intact mice. Double staining of tumors for PAP and AR demonstrated a population of cells that were positive for PAP but negative for AR expression located in hypoxic areas near necrosis. CONCLUSIONS: Our findings demonstrated that PAP is expressed early in normal human fetal prostate development prior to the secretion of significant androgens or expression of AR. In mouse xenografts and human PCa bone metastases, androgens did not significantly regulate PAP expression. These data demonstrate that PAP is a marker of early progenitor cells in the normal prostate and is persistently expressed after castration. PAP may be a suitable target for the treatment of castration-resistant metastatic disease.

Diabetes Mellitus and Glucose Metabolism

ISLETS, LIVERS, PLACENTA, AND VASCULATURE — THE MULTITISSUE IMPACT OF DIABETES

A Novel ERRα-Dependent Insulin Signaling Pathway

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OR14-04

Insulin resistance, a condition in which a cell, tissue, or organism fails to respond appropriately to insulin, is a hallmark for the development of type 2 diabetes and a major