MON-257

Axenfeld-Rieger syndrome (ARS) is an autosomal dominant disorder presenting with abnormal eye development, which leads to glaucoma related blindness in 50% of individuals. Associated mutations affect the transcription factors pituitary homeobox 2 gene (PITX2) and forkhead box C1 gene (FOXC1). Three types of ARS have been described. PITX2 mutation causes ARS type I, which is associated to systemic malformations, including dental hypoplasia, redundant periumbilical skin, and growth hormone deficiency (GHD).

This is the case of a 28-year-old male diagnosed with GHD during childhood. He was referred to a pediatric-endocrinologist at age 10 due to short stature. Evaluation showed a height-for-age curve below the 10th percentile. Physical examination with prominent forehead, decrease visual acuity, maxillary hypodontia, umbilical hernia, and delayed sexual maturity. Testing with reduced IGF-1 and delayed bone age. Clonidine GH stimulation confirmed the diagnosis of GDH. He was treated with somatropin, until linear growth decreased to ½ inch per year at age 16. GHD etiology was never established. At age 26, he developed progressive decrease in visual acuity. Ophthalmology evaluation disclosed polycoria, megalocornea and increase intraocular pressure, suggestive of ARS. Patient was referred to our endocrinology clinics for follow up of previous diagnosis of GHD. Based on clinical findings and history, sequence analysis and deletion/duplication testing of FOXC1, PAX6 and PITx2 were performed, with results positive for pathogenic variant PITX2, Exon 5, c.363_364delinsAA. Assessment of pituitary hormone axis was normal, and no persistent GHD found. No family members exhibited clinical signs of ARS.

Axenfeld-Rieger syndrome is a rare genetic disease. PITX homeodomain transcription factors are critical for the development of the anterior segment of the eye and pituitary. Most mutations in PITX2 affect DNA binding and transactivation that leads to defects in cell proliferation and differentiation of the Rathke's pouch. As a result, GHD may ensue. ARS patients are usually diagnosed during childhood after the development of vision abnormalities. The diagnosis remains primarily clinical upon identification of ocular abnormalities in the iris and cornea, and increased intraocular pressure. Systemic changes are rare findings in ARS, but may include face and tooth abnormalities and isolated growth hormone deficiency. Genetic diagnosis is based on identification of mutations. An adequate management of ARS requires a multidisciplinary approach. Although ophthalmologists usually diagnose this condition, some patients initially present with isolated growth impairment. This may lead to a delay in ophthalmologic evaluation and management. Thus, in patients with GHD of unknown etiology, it is important to have a high index of suspicion of ARS in order to decrease morbidity from vision loss.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Novel Germline p.Gly42Arg MEN1 Missense Mutation in a Family Harboring Very Aggressive Pancreatic Tumor, Hyperparathyroidism and Pituitary Tumor

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SUN-916

Background. Pancreatic neuroendocrine tumors ocurs in 30-80% of patients with MEN-1, and may be non-functioning and hormone secreting tumors. Non-functioning GEP-NETs are increasingly recognised due to advanced imaging modalities such as endoscopic ultrasound thus became the most common type in MEN1 patients. Several mutations MENIN gene were described, although patients with missense mutations are considered as low-impact mutation carriers.**Case report.**Index case, female, 47 years old, menarche at age of 16yo, amenorrhea until 23yo, when started continuous oral contraceptives. At age of 45 presented dizziness, paresthesia, cramps, had the diagnosis of Hyperparathyroidism related to multinodular parathyroid hyperplasia (Calcium 14mg/dL, PTH 117 pg/mL) and macroprolactinoma (prolactin 235 ng/mL; pituitary tumor 1.2 X 1.0 cm). All siblings and her mother were recruited and one brother, aged 45 years confirmed the diagnosis of hyperparathyroidism and nephrocalcinosis. Their mother, aged 77 years old, presented abdominal pain, and had the diagnosis of aggressivepancreatic tumor compressing bile duct causing intra and extra-pancreatic dilation, associated with metastatic lymph nodes. She was sunmitted to total pancreato-gastrectomy with esophagus jejunum anastomosis. **Genetic screening:***MEN1*genetic screening for mutations was performed in all patients. In these probands, MLPA analysis was performed to detect large deletions of the *MEN1*gene, using SALSA MLPA probemix kit P017-D1 according to the manufacturer's instructions (MRC-Holland, Amsterdam, The Netherlands).DNA was extracted from EDTA-Whole blood using MagNA Pure 24 (Roche). Sequencing libraries were qualified/quantified using TapeStation4200 (Agilent). Test method included coding regions ±10bp flanking intronic sequences of 3921 genes enriched using Kappa HyperPlus Library Preparation Kit (Roche) and SeqCap EZ inherited disease panel (Roche) and sequenced (2x75-bp Mid Output V2 Reagent) using NextSeq-500 (Illumina) (estimated mean coverage-100X). Read alignment, variant calling, variant filtration and annotation were performed with Varstation. SNVs and small indels (20bp) with total-read-depth,10X and variant-read-frequency more than20% found on AIP, APC, CDC73, CDKN1B, DICER1, FH, MAX, MEN1, MET, NF1, PRKAR1A, PTEN, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TP53, VHL, WRN genes were analyzed.A missense mutation in exon 2, MEN1:c.124G.C:p.(GLY42Arg) was detected. **Discussion and conclusion:**MEN1-associated GEP-NETs seem to have a low proliferation rate and long survival has been reported, they should be of particular attention, since they are still the principal cause of death in MEN1 patients.Early screening and diagnosis are crucial for MEN-1 phenotypes.

Tumor Biology

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

Functional Characterization of Tumor-Associated Germline TMEM127 Variants Reveals Novel Insights