Different Endocrine Affects in DICER-1 Syndrome

Aslıhan Araslı Yılmaz[1], Zehra Aycan[1 2], Şenay Savaş Erdeve[1], Semra Çetinkaya[1]

1-Dr.Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital, Pediatric Endocrinology Department , Ankara, Turkey
2-Ankara University Medicine Faculty, Pediatric Endocrinology Department, Ankara, Turkey

DICER1 syndrome is a pleotropic, autosomal dominant familial genetic tumor predisposition syndrome. DICER1 somatic + germ-line mutations (double hit hypothesis); cystic nephroma; pleuropulmonerblastoma, ovarian sex cord-stromal tumors, multinodular goitre (MNG) are associated with many conditions such as differentiated thyroid cancer, pituitary blastoma. We presented three cases, two of whom were siblings, who had been consulted because of non-menstruation and goitre and had the same diagnosis despite their different characteristics.

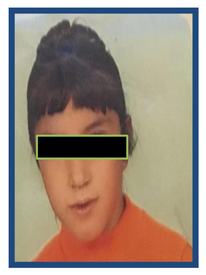
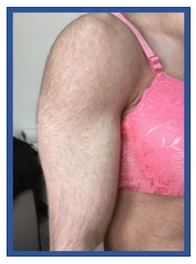
CASE PRESENTATION

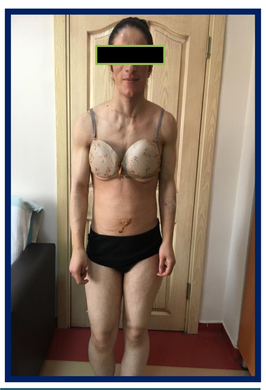
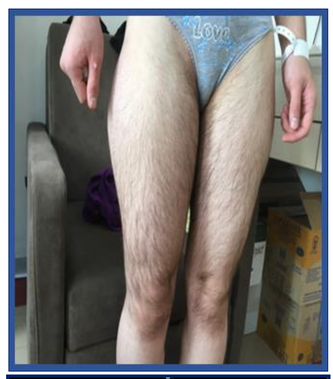
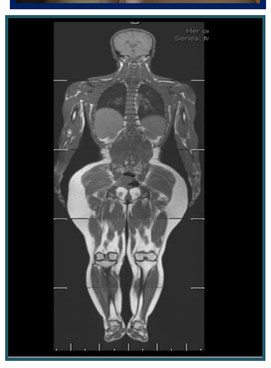
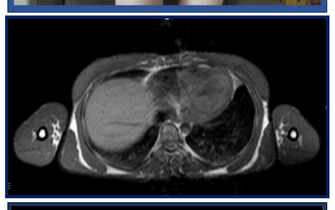
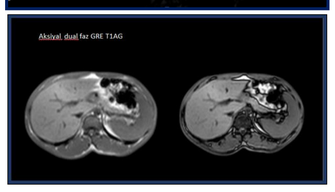
Case 1-History

15 year old girl,
-Menstrual irregularity,
-Hairing increase
-Neck swelling
She weighted 3000 gr at birth.
10 years old-Appendectomy
Grand mother died of uterine cancer

Case 1-Physical Exam

BMI:26,5 kg/m2
Goitre + No acanthosis
Bilateral breast hypoplasic - Puberty: TannerV-
Cliteromegaly Ø FGS: 34-
Loss of buccal fat pads on face
Muscular appearance of arms and legs
Increased fat tissue in lower extremity and gluteal region

Case 1-Laboratuary-Imaging

Hyperandrogenism
Standard Dose ACTH test: Normal
Mild Triglyceride excess OGTT: Insulin Resistance+
TFT: Euthyroid-Thyroid autoantibodies (-)

Leptin: 3,18 ng/ml

C3 Low +
Autoimmune disease screanings: Negative
LMNB2: Mutation negative

Case 1-Laboratuary-Imaging

Pelvic US: Ovary sizes increased; no PCOS view
Surrenal USG: Normal
Abdomen USG: Grade 1 Hepatosteatosis
Thyroid US: Gland hyperplasic-solid and cystic multiple nodules with the largest 2cm

Whole Body MR-MR Spectroscopy:
Compatible with acquired partial lipodystrophy

Case 1-Laboratuary-Imaging

FNAB: Follicular Neoplasia - -> Bilateral near total thyroidectomy -> Residual tissue growth + Increase in nodules ->
Post-op 12th month: Hyperandrogenism + increased tumor markers despite metformin !!!!
Pelvic USG: A significant solid mass of 120 mm in size, with the right ovary size increasing, and the largest 75 x 60 mm cystic necrotic area, completely filling the ovary

SERTOLI-LEYDIG CELL TUMOUR

Case 1-Laboratuary-Imaging

Sertoli Leydig Cell Tumor: c.5113G> A; p.E1705K) hot-spot mutation

MNG: c.5125g> A; p. D1709N hot-spot mutation
Germ-line mutationØ -> MLPA

Case 2

She was referred to the goiter at the age of seven years.
Left hemiparesis secondary to birth trauma +Operated multicystic nephroma and neuroblastoma at 14 months of age.
Thyroid diffuse palpable + 2cm moving soft nodule on the right +
TFT: Euthyroid-Thyroid auto ab negative Thyoglobulin> 1000 ng / dl
Thyroid US: Thyroid gland sizes increased- the largest of both lobes is 21x13 mm and 18x16 mm cystic, multiple heterogeneous isoechoic -solid nodules +
FNAB: Follicular Neoplasia -> Right total /Left near total thyroidectomy
Pathology: Nodular hyperplasia

New nodule in residual tissue

Last FNAB: Follicular Neoplasia –Complemantary total thyroidectomy ->Noduler hyperplasia

Case 3

6 years old girl
Her sister has a goitre.
Physical Examination:No feature
TFT euthyroid - Thyoglobulin and calcitonin normal
Thyroid US: Normal gland volume
12 x 7 x 9 mm cystic hyperechoic-heterogeneous solid in the right lobe middle section nodular lesion
First FNAB: Benign +

New nodule development
Increase in nodule size and number

Last FNAB:Atypia of undetermined significance -> Total thyroidectomy
Pathology: Nodular hyperplasia –Papiller carcinom suspicion
Germline mutation+ Somatic mutation examination was planned.

DICER 1 GENE, a germline mutation was detected in exon 23 c.4566_4570dupCTTTG (her father and sister carrier).

MNG: RNase IIIb somatic hotspot mutation,c.5438A> T c.5439G> C ve c.5439G> T (p.E1813D)
Proband CN: (c.5113G> A, p.E1705K) second somatic RNase IIIb hot spot mutation

Conclusion: Although DICER1 syndrome is a tumor predisposition syndrome, it can also perform endocrine effects (MNG, differentiated thyroid cancer, ovarian sex cord-stromal tumors, pitutier blastoma-related diabetes insipitus / Cushing's disease. Here previously not reported rare cases with acquired partial lipodystrophy are presented which had similar features of MNG.

References:
1-Solarski, Michael, et al. "DICER1 gene mutations in endocrine tumors." *Endocrine-related cancer* 25.3 (2018): R197-R208.
2-de Kock, Leanne, et al. "Deep sequencing reveals spatially distributed distinct hot spot mutations in DICER1-related multinodular goiter." *The Journal of Clinical Endocrinology & Metabolism* 101.10 (2016): 3637-3645.
3-Khan, Nicholas E., et al. "Quantification of thyroid cancer and multinodular goiter risk in the DICER1 syndrome: a family-based cohort study." *The Journal of Clinical Endocrinology & Metabolism* 102.5 (2017): 1614-1622

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