The Turkish Journal of Pediatrics 2021; 63: 500-505
https://doi.org/10.24953/turkjped.2021.03.018

Case Report

Sertoli-Leydig cell tumor, thyroid follicular carcinoma and rhabdomyosarcoma of the uterine cervix in a prepubertal girl with pathogenic germline variant in *DICER1* gene

İbrahim Karnak[1], Ahmet Cevdet Ceylan[2], Mithat Haliloğlu[3], Alev Özön[4], Diclehan Orhan[5], Tezer Kutluk[6]

Departments of [1]Pediatric Surgery, [3]Radiology, [4]Pediatric Endocrinology, [5]Pathology, [6]Pediatric Oncology, Hacettepe University Faculty of Medicine, Ankara; Department of [2]Medical Genetics, Ankara City Hospital, Ankara, Turkey.

ABSTRACT

Background. DICER1 syndrome is a hereditary cancer predisposition syndrome which is related *DICER1* gene and may present a variety of manifestations.

Case. A prepubertal girl with ovarian Sertoli-Leydig cell tumor, thyroid follicular carcinoma, embryonal rhabdomyosarcoma of the cervix and lung cyst is presented. Genetic analysis demonstrated mutation (c.3377delC, c.71delC) in 14q32.13 loci and confirmed the diagnosis of DICER1 syndrome.

Conclusion. The case is presented to emphasize the importance of early diagnosis of alterations in *DICER1* gene and close follow-up for the development of DICER1 syndrome related pathologies, and necessity for genetic evaluation of the family.

Key words: Sertoli-Leydig cell tumor, differentiated thyroid carcinoma, rhabdomyosarcoma, DICER1 syndrome, lung cyst.

The human DICER1 gene contains 27 exons, encodes 1922 amino-acid long protein and it is located on chromosome 14q32.13. It is a ribonuclease (RNase) III endoribonuclease and a key component of the RNA interference pathway.[1]

Pathogenic germline *DICER1* variants cause a hereditary cancer predisposition syndrome, DICER1 syndrome, with a variety of manifestations including pleuropulmonary blastoma (PPB), ovarian sex-cord stromal tumors, particularly Sertoli-Leydig cell tumor (SLCT), lung cysts, cystic nephroma (CN), renal sarcoma and Wilms' tumor, nodular hyperplasia of the thyroid, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma, genitourinary embryonal rhabdomyosarcoma (ERMS) and brain tumors such as pinealoblastoma and pituitary blastoma.[1-5]

This case is a prepubertal girl initially presented with macrocephaly, SLCT, thyroid nodule and lung cyst. Extremely rare coexistence of two rare pathologies raised the possibility of common pathogenetic pathway, possibly *DICER1* related pathogenesis. The authors share their experience on this illustrative case of DICER1 syndrome to stress the necessity of intensive work to investigate the components of this syndrome and close follow up of the child for the development of other DICER1 associated pathologies.

Case Report

A 5-year 10-month-old girl was admitted for right ovarian mass. The mass was diagnosed by ultrasonography (US) examination during

✉ İbrahim Karnak
ikarnak@hacettepe.edu.tr

Received 7th May 2020, accepted 28th September 2020.

evaluation for urinary tract infection. Physical examination revealed a fullness on palpation of the suprapubic region, and a mobile mass in the Douglas's pouch on rectal touch. An asymptomatic thyroid nodule (2 x 1.5cm) in the right thyroid lobe was also diagnosed incidentally during palpation of the neck. The family medical history revealed Hashimoto's thyroiditis in maternal aunt, and goiter with benign nodule in maternal grandmother.

Magnetic resonance (MR) imaging showed lobular, solid-cystic mass of 7.2 x 6.3 x 5.5 cm size in the rectouterine pouch and normal ovaries. Ultrasound of the neck revealed a solid nodule (2 x 1 cm) in the right thyroid lobe, a cystic nodule (0.4 x 0.4 cm) in the left thyroid lobe and reactive lymph nodes.

Alpha-feto protein (2.72 ng/ml; N: 0-9), beta-HCG (<0.5 mIU/ml), total testosterone (<0.02; N: 0.06-0.82 ng/ml), FSH (1.48 mIU/ml, N), LH (<0.1 mIU/ml; N), estradiol (<5 pg/ml; N: <20), free-T4 (14.23 pmol/L; N: 7.86-14.41), TSH (2.01 μIU/ml; N: 0.34-5.6), thyroglobulin (35.5 ng/ml; N: 1.15-50) levels, complete blood count and blood biochemistry were within normal ranges.

At operation, a Pfannenstiel incision was used. Intraperitoneal fluid was sampled for cytology, a solid mass (8 x 8 cm) originating from right ovary was excised completely with a rim of normal ovarian tissue. Left ovary was normal in appearance and normal consistency on palpation. Omentum was excised and peritoneum was sampled. Fine needle aspiration and tru-cut biopsies were taken from the nodule in the right thyroid lobe. Postoperative course was uneventful.

Pathology report confirmed moderately differentiated Sertoli-Leydig cell tumor of the ovary with clear surgical margins (Fig. 1). Peritoneal fluid, omentum and peritoneum were tumor free. The thyroid nodule was a benign follicular lesion. No further treatment was given due to the stage I disease.

Postoperative computerized tomography of the thorax revealed an air cyst (25 x 20 x 20 mm) in the left lower lobe of the lung (Fig. 2). Postoperative control MR images showed no residual or recurrent tumor in the abdomen, and normal appearing ovaries bilaterally.

The patient was under close follow-up and control thyroid ultrasound revealed a solid nodule (17 x 18 x 27 mm) in the right lobe and 2 nodules (5 x 5.5 x 10 mm solid and 15 x 7 x 9 mm cystic) in the left lobe of the thyroid. The patient underwent a right thyroid lobectomy and excision of both nodules from left lobe of the thyroid. Frozen section of all tissues was reported as free of malignant tissue. However permanent sections showed a differentiated thyroid carcinoma area in the right lobe nodule and a complementary thyroidectomy was performed later. Histopathology of the remaining thyroid demonstrated follicular carcinoma in the left lobe nodule with capsular invasion (Fig. 3). Postoperative thyroid scan revealed no residual tissue or pathological

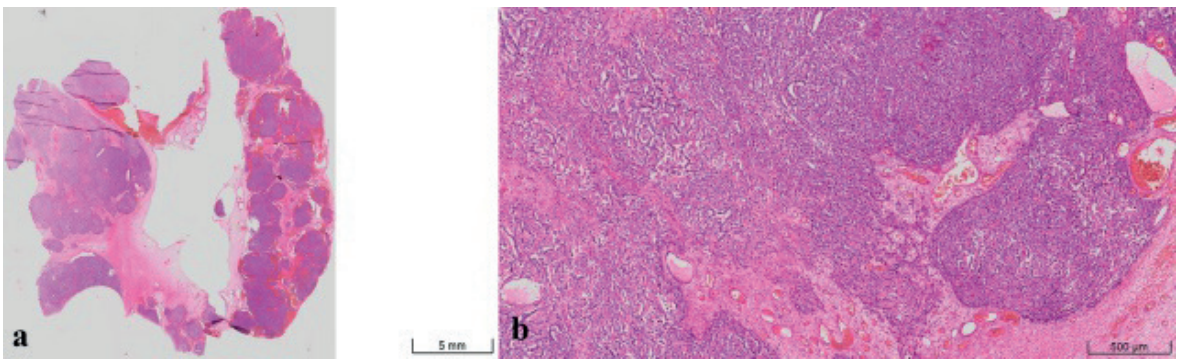

Fig. 1. Moderately differentiated Sertoli-Leydig cell tumor showing a lobulated pattern **(a)**. Sertoli cells forming tubules and cords admixed with small clusters of Leydig cells **(b)**.

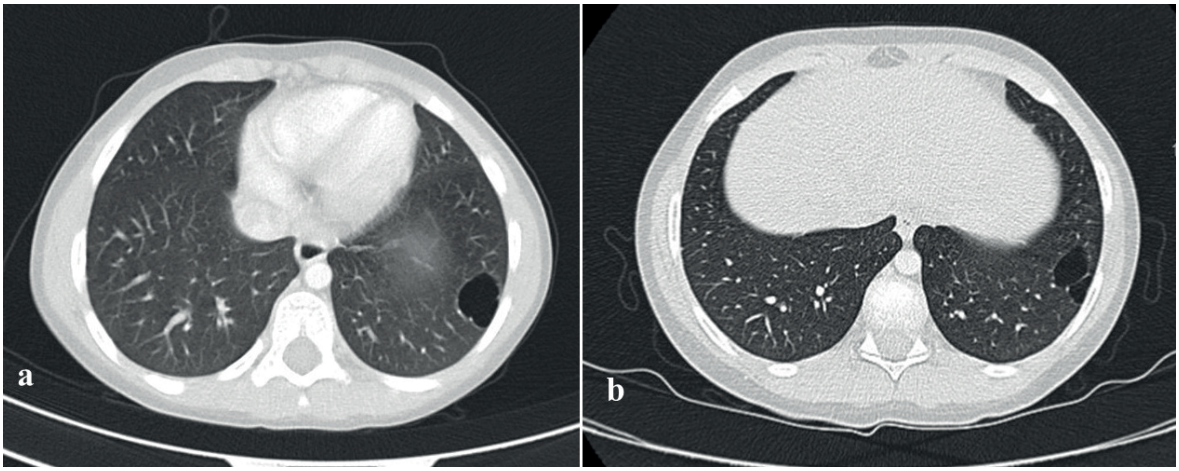

Fig. 2. Thorax CT revealed stabile air cyst in the left lower lobe of the lung, at the time of diagnosis **(a)** and after 2 years **(b)**.

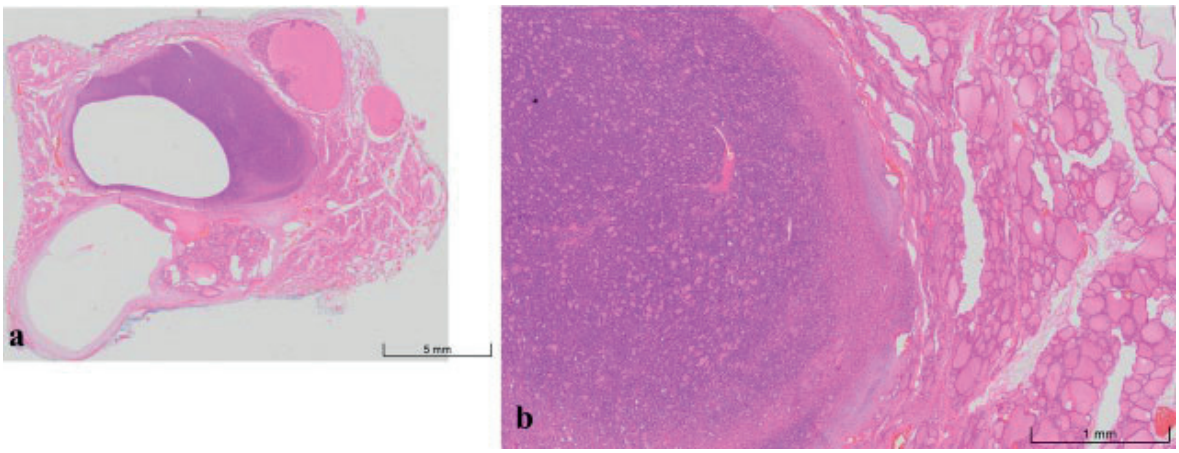

Fig. 3. Follicular carcinoma with microfollicules **(a)** and capsular invasion **(b)**.

lymph node and radioactive iodine-131 ablation was performed.

Two years later from ovary preserving surgery, the patient admitted with vaginal bleeding of one-month duration. Cysto-vaginoscopy revealed a polypoid lesion (2.5 x 1.5 cm) protruding from cervical ostium into the vagina and this polypoid lesion was excised totally. Histopathological evaluation reported as botryoid rhabdomyosarcoma (Fig. 4). She received VAC (ARST0331) regimen for 24 weeks. She is currently free of disease and under follow up with stable pulmonary air cyst.

The next generation sequencing revealed c.3377delC (p.Thr1126fs*18) at *DICER1* (NM_177438.2) classified as pathogenic germline variant. The parents and sister of the index patient were recommended for detailed genetic analyses for DICER1 status.

The parents of the patient were informed about the preparation of an article and an informed consent was obtained from parents.

Discussion

DICER1 syndrome is inherited as an autosomal dominant disease which is associated with germline mutations in *DICER1*. This syndrome consists of PPB, SLCT of the ovary, genitourinary embryonal RMS, lung cyst, thyroid nodule or differentiated thyroid carcinoma, pituitary

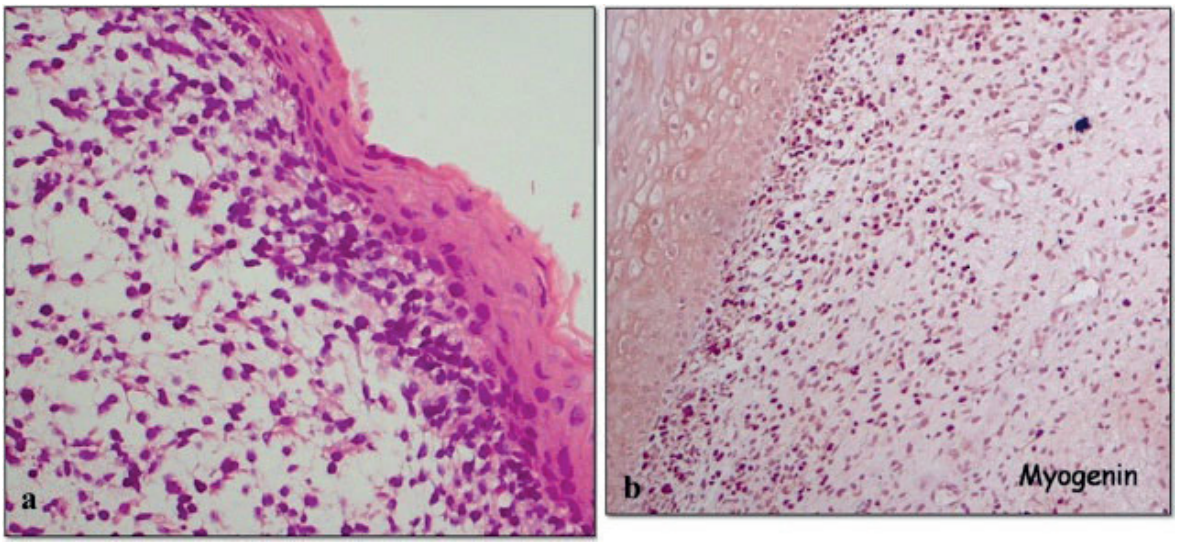

Fig. 4. Botryoid rhabdomyosarcoma with cambium layer beneath intact epithelium and rhabdomyoblasts on a loose myxoid stroma **(a)**. Myogenin positive tumor cells in cambium layer **(b)**.

blastoma or pinealoblastoma. Macrocephaly may be seen as a non-tumoral expression in DICER1 syndrome patients.[1]

Sertoli-Leydig cell tumor of the ovary is a rare tumor in children and coexisting thyroid nodule is highly unusual even in a high pediatric surgical and oncological patient volume hospital. The history of thyroid disease in relatives prompted us for close follow up of the patient and was considered highly suggestive for DICER1 syndrome. Sertoli-Leydig cell tumor of the ovary was treated by ovary-sparing surgery. Intermediate differentiation of tumor, clear margins and tumor free peritoneum and as well as peritoneal fluid suggested low stage disease requiring no additional treatment for SLCT. The diagnosis of thyroid malignancy necessitated complementary thyroidectomy and radioactive iodine-131 ablation therapy.

Pleuropulmonary blastoma is a rare pathology, in spite of being the most common primary lung malignancy in children. It can progress from a multicystic lesion (Type I) to mixed solid-cystic (Type II) and solid stage (Type III) tumors. A fourth type of PPB, Type Ir "regressed" is not malignant. Therefore, it should be kept in mind that pulmonary cystic lesion in a child with pathogenic DICER1 variant can be Type I PPB until proven otherwise. The lung cyst has been asymptomatic and stable radiologically for 4 years in our patient. Since we do not have histological evaluation of the lung cyst in our patient, the lesion is under regular follow up by chest X-rays and CTs.

Only a few children with SLCT and thyroid pathology, with or without associating genitourinary ERMS, has been reported to date.[6-11] Our patient developed embryonal RMS of the cervix and was treated by endoscopic surgery and chemotherapy.

The genetic evaluation for *DICER1* status is required for every child with SLCT, PPB or CN and/or accompanying thyroid pathology.[12] It has been suggested that *DICER1* mutation poses a low-risk of malignancy and *DICER* sequencing and gene dosage determination is recommended in molecular analysis of pediatric thyroid specimens.[13] Additionally, *DICER1* sequencing has been recommended in children with multinodular goiter, multiple multinodular goiter cases within the same family, or its association with benign or malignant tumors.[14]

Once a pathogenic variant is diagnosed in *DICER1*, follow up process of the patients is

quite stressful for the clinician and the family members. The family members should be informed about the syndrome as well as the signs and symptoms of possible pathologies, and the clinician should be alert during surveillance and follow up.

A chest X-ray at birth, every 4-6 months until 8 years of age and every 12 months for 8-12 years of age and a chest CT at 3-6 months of age has been recommended for investigation of lung pathologies in a child with *DICER1* syndrome.[2] The recommendations for screening thyroid pathology is baseline thyroid US by 8 years of age then every 3 years or with suspicious symptoms/findings on physical examination. If the child receives chemotherapy or radiotherapy, a baseline US of the neck, and then annual US for 5 years, followed by US every 2 to 3 years is recommended if no nodules are detected initially.[2]

It has been recommended that female reproductive tract should be checked by pelvic and abdominal US every 6-12 months beginning at 8 - 10 years of age until at least 40 years, by keeping the information in mind that the current oldest patient with *DICER1*-associated SLCT is 61 years old. Our case demonstrates that *DICER1*-associated SLCT can be encountered in younger ages and baseline US examinations should be performed before 8 years of age. Our case will be followed up by US for the development of metachronous or recurrent genitourinary neoplasms till the recommended ages.[2] *DICER1*-associated renal pathologies can be investigated by abdominal US every 6 months until 8 years of age, then every 12 months until 12 years of age.[2]

The patient should be checked by physical examination as well as detailed ophthalmologic examinations from 3 years of age through to at least 10 years of age. Urgent MRI has been recommended for any symptom of intracranial pathology.[2] Bueno et al.[15] suggested annual whole-body MR, chest X-ray and US examination of the target body system for at-risk pediatric patients with *DICER1* syndrome.

The pediatric oncological and pediatric surgical professionals should have information about *DICER1*-related pathologies. *DICER1* status should be determined in every child with SLCT, PPB or CN, and/or accompanying thyroid pathology. The parents of children with *DICER1* syndrome should be aware of signs and symptoms suggestive for *DICER1*-related pathologies.

Author contribution

İbrahim Karnak, surgical treatment, writing, editing, orginizations for genetical analysis Ahmet Cevdet Ceylan, genetical analysis, genetic counsulling, writing Mithat Haliloğlu, detailed evaluation of radiological examinations, writing, editing Alev Özön, detailed endocrinological evaluation and follow up, writing, editing Diclehan Orhan, histopathological evaluation, writing, editing Tezer Kutluk, oncological treatment, writing, editing, follow up, mentorship.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. de Kock L, Wu MK, Foulkes WD. Ten years of DICER1 mutations: provenance, distribution, and associated phenotypes. Hum Mutat 2019; 40: 1939-1953.
2. Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. Clin Cancer Res 2018; 24: 2251-2261.
3. Durieux E, Descotes F, Mauduit C, Decaussin M, Guyetant S, Devouassoux-Shisheboran M. The co-occurrence of an ovarian Sertoli-Leydig cell tumor with a thyroid carcinoma is highly suggestive for a DICER1 syndrome. Virchows Arch 2016; 468: 631-636.
4. Schultz KA, Yang J, Doros L, et al. DICER1-pleuropulmonary blastoma familial tumor predisposition syndrome: a unique constellation of neoplastic conditions. Pathol Case Rev 2014; 19: 90-100.

5. Abbo O, Pinnagoda K, Brouchet L, et al. Wilms tumor, pleuropulmonary blastoma, and DICER1: case report and literature review. World J Surg Oncol 2018; 16: 164.

6. Moke DJ, Thomas SM, Hiemenz MC, et al. Three synchronous malignancies in a patient with DICER1 syndrome. Eur J Cancer 2018; 93: 140-143.

7. de Kock L, Hillmer M, Wagener R, et al. Further evidence that full gene deletions of DICER1 predispose to DICER1 syndrome. Genes Chromosomes Cancer 2019; 58: 602-604.

8. Haley M, Bindal P, McAuliffe A, Vredenburgh J. A family with Sertoli-Leydig cell tumour, multinodular goiter, and DICER1 mutation. Curr Oncol 2019; 26: 183-185.

9. McClean GE, Kurian S, Walter N, Kekre A, McCluggage WG. Cervical embryonal rhabdomyosarcoma and ovarian Sertoli-Leydig cell tumor: a more than coincidental association of two rare neoplasms? J Clin Pathol 2007; 60: 326-328.

10. Dehner LP, Jarzembowski JA, Hill DA. Embryonal rhabdomyosarcoma of the uterine cervix: a report of 14 cases and a discussion of its unusual clinicopathological associations. Mod Pathol 2012; 25: 602-614.

11. Sunku R, Duggal R, Patel FD, Rai B, Srinivasan R, Nijhawan R. Cervical embryonal rhabdomyosarcoma and ovarian Sertoli-Leydig cell tumor with congenital absence of unilateral ovary. J Cancer Res Ther 2015; 11: 654.

12. Faure A, Atkinson J, Bouty A, et al. DICER1 pleuropulmonary blastoma familial tumour predisposition syndrome: what the paediatric urologist needs to know? J Pediatr Urol 2016; 12: 5-10.

13. Wasserman JD, Sabbaghian N, Fahiminiya S, et al. DICER1 mutations are frequent in adolescent-onset papillary thyroid carcinoma. J Clin Endocrinol Metab 2018; 103: 2009-2015.

14. Oliver-Petit I, Bertozzi AI, Grunenwald S, et al. Multinodular goiter is a gateway for molecular testing of DICER1 syndrome. Clin Endocrinol (Oxf) 2019; 91: 669-675.

15. Bueno MT, Martinez-Rios C, la Puente Gregorio A, et al. Pediatric imaging in DICER1 syndrome. Pediatr Radiol 2017; 47: 1292-1301.