A family with Sertoli–Leydig cell tumour, multinodular goiter, and DICER1 mutation

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ABSTRACT

Background DICER1 syndrome is an autosomal dominant tumour predisposition syndrome associated with a wide variety of cancerous and noncancerous conditions, including ovarian sex cord–stromal tumours and thyroid conditions, including multinodular goiter. The most common ovarian sex cord–stromal tumour associated with DICER1 syndrome is Sertoli–Leydig cell tumour, with germline DICER1 mutations present in more than 50% of cases. We present a case in which a patient in her late 30s was diagnosed with a Sertoli–Leydig cell tumour in the background of a strong family history of multinodular goiter and Sertoli–Leydig cell tumour with a germline mutation in DICER1.

Case Presentation A 38-year-old woman with history of multinodular goiter was found to have stage IIIC ovarian Sertoli–Leydig cell cancer after presenting with abdominal pain. She underwent multiple surgeries and chemotherapy. The patient developed rapid disease progression and died 7 months after diagnosis. Seven years earlier, a daughter had experienced the same disease and was found to have a germline DICER1 mutation. The mother had not undergone testing before her own diagnosis.

Summary The co-occurrence of Sertoli–Leydig cell tumour and multinodular goiter is highly suggestive of DICER1 syndrome. The recognition of DICER1 syndrome within a family is essential for increased awareness and potential early recognition of complications. Most conditions associated with DICER1 syndrome occur in childhood, and most of the current screening recommendations are specific for childhood and young adulthood. Cancer risks and findings for the adult population are not as well defined. Clinicians who encounter DICER1 syndrome should review recommendations for genetic testing and surveillance and enrol patients in the DICER1 registry.

Key Words DICER1, microRNA, sex cord–stromal tumour, Sertoli–Leydig, multinodular goiter, genetic mutation

BACKGROUND

Ovarian tumours are classified into 3 main types, the most common being epithelial, followed by germ-cell and sex cord–stromal tumours. Sex cord–stromal tumours represent 8% of all ovarian tumours and include Sertoli–Leydig cell tumours (SLCTs). Sertoli–Leydig cell tumours are very rare, accounting for fewer than 0.5% of all ovarian tumours. They contain Sertoli and Leydig cells, which are somatic cells in male gonads, presenting a pseudo-male gonadal genesis in the ovary. Sertoli–Leydig cell tumours can therefore present with androgenic symptoms. They are typically unilateral and large in size. Less than 20% display malignant behaviour. In DICER1 syndrome, SLCTs are the most commonly observed sex cord–stromal tumour. The mortality rate with SLCTs is low, representing fewer than 5% of the recorded deaths associated with DICER1 syndrome.

Sertoli–Leydig cell tumours can be well, moderately, or poorly differentiated. Well-differentiated SLCTs are often DICER1-independent, while the moderately and poorly differentiated types often co-exist with one another and typically have a DICER1 mutation. The international Ovarian and Testicular Stromal Tumour Registry has shown that a germline DICER1 mutation is present in more than 50% of female patients with SLCT.

Individuals with DICER1 syndrome have an increased risk of multinodular goiter (MNG) and differentiated thyroid cancer. Multinodular goiter is a frequent manifestation of DICER1 syndrome. The overall incidence of MNG or thyroidectomy by 20 years of age is 32% in female patients and 13% in male patients with DICER1 syndrome, compared with 0% in male and female control subjects. Individuals with a DICER1 mutation have a risk of developing thyroid cancer 16–24 times that in the general population.
Thyroid cancer associated with DICER1 syndrome is usually differentiated, of follicular or papillary origin, and typically behaviourally indolent7.

DicER1 is a RNAse III endonuclease involved in the generation of double-stranded microRNA (miRNA) that affects gene expression post-transcriptionally5. It has 2 functional enzymatic domains: RNAseIII and RNAseHB. Most DICER1 syndrome tumours have one allele with a germline nonsense or frameshift mutation resulting in loss of function; the other allele has a somatic missense mutation within 5 known hotspots within RNAseHB2,6,10. Of all ovarian SLCTs, 50%–60% occur in carriers of germline DICER1 mutations. Nearly all moderately or poorly differentiated SLCTs harbour a somatic mutation in 1 of the 5 hotspots2–4. Those mutations result in improperly cleaved 5p miRNAs from pre-miRNA hairpin structures, which result in an abnormal ratio of 5p to 3p miRNAs, ultimately affecting downstream target expression6. The situation is similar to a 2-hit tumour suppressive model; however, the 2nd somatic “hit” creates a partially functional allele with a miRNA biogenesis bias. Systemic loss of 5p miRNAs can cause pseudodifferentiation of testicular elements and oncogenic transformation in the ovary2. Current data suggest that about 80% of people with a DICER1 mutation inherit the mutation from a parent; in the remaining 20% of cases, the mutation likely appears de novo11.

We present a patient with a history of MNG who was diagnosed with a SLCT in the background of a strong family history of SLCT and MNG in her daughters.

CASE PRESENTATION

A 38-year-old woman with history of MNG, gastric bypass surgery, and iron and vitamin B12 deficiencies presented to the emergency department with sharp left-sided abdominal pain. The patient otherwise felt well and had not noted any other changes. Computed tomography imaging of her abdomen and pelvis showed a massive, complex, solid and cystic mass occupying most of the right side of the abdomen. The mass was 25 cm in its largest dimension, consistent with a complex ovarian neoplasm without evidence for metastatic disease to the chest, abdomen, or pelvis. The patient was referred to gynecology, where transvaginal and pelvic ultrasonography confirmed the findings. Serum cancer antigen 125 was elevated at 122.3 U/mL.

The patient subsequently underwent cystoscopy and bilateral ureteral stenting, followed by an exploratory laparotomy with lysis of adhesions, right salpingo-ophorectomy, tumour debulking, and appendectomy. Pathology examination of the tumour revealed a malignant moderately-to-poorly differentiated Sertoli–Leydig tumour. Cytology from the patient’s abdominal fluid showed atypical cells. The patient’s malignancy was therefore classified as stage IIIIC.

The patient was referred to medical oncology. She was consented to 6 cycles of adjuvant bleomycin–etoposide–cisplatin chemotherapy after her baseline pulmonary function and diffuse capacity of the lungs for carbon monoxide had decreased to 62% from 82%. Bleomycin was therefore omitted from the subsequent cycles of chemotherapy. Cycles 4 and 5 were complicated by prolonged nausea, severe anemia, and thrombocytopenia warranting a dose reduction in etoposide. Restaging with cycle 5 demonstrated no evidence of progression. The patient was able to complete a total of 6 cycles.

After completion of chemotherapy, the patient underwent definitive debulking surgery, which involved total abdominal hysterectomy, left salpingo-ophorectomy, and omentectomy. Several biopsies were performed. Of 8 samples submitted for biopsy, 1, a rectosigmoid mass, was positive for microscopic metastatic disease.

The patient was monitored after surgery with initial plans for further chemotherapy or a clinical trial (or both). However, her recovery was complicated, and she was not fit for chemotherapy at that time. Unfortunately, she developed significant and rapid progression of her disease 2 months postoperatively. Because of her multiple post-operative complications and poor performance status, she was not a candidate for further treatment, and she died 7 months after diagnosis.

Notably, the patient had a complex family history of ovarian tumours and MNG. Her youngest daughter had a history of SLCT diagnosed at the age of 7 years and had received 6 cycles of bleomycin–etoposide–cisplatin chemotherapy adjuvantly, with achievement of remission. Said daughter had undergone genetic testing at the time of her SLCT diagnosis and was found to have a pathogenic germline mutation c.325C>T(p.Gin109*) in DICER1. The patient’s other daughter had been diagnosed with MNG by the time of her mother’s diagnosis, and the patient’s mother had a history of an unknown ovarian tumour.

Given her family history, the patient was referred to a genetic counsellor after her SLCT diagnosis. She was found to carry the same deleterious germline mutation in DICER1 found in her daughter. The patient’s second daughter has since had a thyroidectomy, and after referral to a genetic counsellor, she was found to have the same DICER1 mutation found in her mother and sister.

DISCUSSION AND SUMMARY

DICER1 syndrome is a rare autosomal dominant, hereditary, pleiotropic tumour predisposition syndrome10. Pathogenic mutations in the DICER1 gene have been associated with the development of cancerous and noncancerous conditions including ovarian sex cord-stromal tumours, cervical embryonal rhabdomyosarcoma, pleuropulmonary blastoma (the leading primary lung cancer in children and the deadliest DICER1 condition), cystic nephroma, Wilms tumour, renal sarcoma, pinealoblastoma, pituitary blastoma, MNG, and thyroid cancer, among others7,11.

Most of the conditions associated with DICER1 syndrome occur in the childhood years, although age distributions vary widely5,7,11. Regardless of phenotype at presentation, all patients and their families should be educated about the wide range of DICER1 diseases, including phenotype, risk, age distribution, and genetic
testing. Family education, genetic counselling, and review of suggested screening guidelines such as those recently proposed by Schultz et al.7 (reflective of the inaugural 2016 International DICER1 Symposium), would lead to sensible testing agreed upon by patient, family, and caregivers. Screening guidelines are not official, with the current recommendations being based on expert opinion. Screening practices must be weighed carefully against the potential morbidities of the screening. Currently, no evidence shows that screening for early diagnosis is beneficial, and further research is needed.

Identifying DICER1 syndrome is clinically important both for the patient and the patient’s family members and potential offspring. Clinicians should be cognizant of the multisystem phenotypes of DICER1 syndrome, because early recognition, together with education, surveillance, and genetic counselling, could lead to earlier detection of complications.

Our patient’s case represented a unique scenario in which a child was diagnosed with DICER1 syndrome before the mother. Unfortunately, the parents were not tested after the daughter’s diagnosis, and the mother’s own DICER1 mutation not discovered until her slCT cancer diagnosis.

As research into DICER1 variants continues, screening, risk stratification, and genetic counselling will have to be updated, and patients and clinicians will both have to be kept abreast of new recommendations. Clinicians who encounter DICER1 syndrome should review available screening guidelines, enrol affected patients into the DICER1 registry, and consider contacting syndrome experts for further guidance.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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