SHORT REPORT

Paediatric ovarian tumours and their associated cancer susceptibility syndromes

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ABSTRACT

Non-epithelial ovarian tumours are rare neoplasms that occasionally arise in childhood and adolescence. They can be associated with various cancer susceptibility syndromes. The morphological overlap seen across these tumours and their rarity can make the diagnosis challenging. In the case of an incorrect diagnosis, the underlying genetic susceptibility may be missed. In this review, we outline the genetic background of ovarian non-epithelial tumours arising in children, emphasizing the genes harbouring pathogenic germline variants associated with each tumour type. Specifically, juvenile granulosa cell tumours, Sertoli-Leydig cell tumours, sex cord tumours with annular tubules, Sertoli cell tumours, germ cell tumours and small cell carcinoma of the ovary of hypercalcaemic type are discussed in this review. For each tumour type, we detail the personal and family history features and the presenting characteristics of the ovarian tumour as well as the pathological features and molecular markers that point towards a cancer predisposition syndrome. Throughout, we stress the need for specialised pathological review in difficult cases.

INTRODUCTION

Ovarian tumours in childhood and adolescence are uncommon and may be associated with cancer predisposition syndromes (CPSs). These tumours are distinguished from those that arise in adulthood by their histological subtypes and by the different CPSs with which they are associated. Clinicians should recognise that an ovarian tumour developing in childhood may be the first sign of a CPS in a family. Diagnosing the CPS offers the important possibility of surveillance for other CPS-related disease in the patient and family.

While many reviews outline the tumours associated with a CPS, very few describe the inverse relationship, that is, when should the clinician suspect a CPS following the diagnosis of an ovarian neoplasm. Here we discuss ovarian tumours that are most likely to arise in childhood and their associated CPSs. We also discuss clinical features that may indicate a higher likelihood of a CPS and cover current screening recommendations for these tumours. It is important to note that the most prevalent ovarian neoplasm associated with a CPS occurs in adults with predisposing *BRCA1/BRCA2* mutations: high-grade serous carcinoma. However, these are epithelial neoplasms and are exceedingly rare in individuals under age 18 years. Mucinous epithelial neoplasms do occur under age 18 years

but are not known to be associated with cancer susceptibility syndromes. Most paediatric ovarian tumours which are associated with a CPS are in the non-epithelial categories.

SEX CORD-STROMAL TUMOURS (SCST)

Juvenile granulosa cell tumour

General aspects

Juvenile granulosa cell tumours (JGCTs) (figure 1A) are rare ovarian tumours, accounting for less than 1% of ovarian neoplasms but accounting for approximately two-thirds of SCSTs presenting in childhood.^{1,2} Just under one-half of JGCTs are diagnosed in the first decade of life and an additional one-third in the second decade.¹ Over 95% of patients present with disease limited to the ovary and these low-stage patients have an excellent prognosis, with >90% overall survival with surgical resection alone.³ Most tumours are unilateral, although 2%–5% of cases are bilateral.^{1,2} A common presenting feature of JGCTs is isosexual precocious pseudopuberty, as these tumours often secrete oestrogen.³ Rarely they are associated with androgenic manifestations.

Key differential diagnoses

The differential diagnosis of JGCT includes other SCSTs and small cell carcinoma of the ovary of hypercalcaemic type (SCCOHT). The SCSTs which are most likely to be morphologically confused with JGCT are adult granulosa cell tumour (AGCT) (figure 1B) and Sertoli-Leydig cell tumour (SLCT) (figure 1C), although occasionally others may enter into the differential diagnosis. Immunohistochemistry (using markers such as inhibin, CD56, FOXL2, steroidogenic factor-1 and calretinin) is useful in diagnosing a SCST but not in distinguishing between the various types (figure 1D). From a molecular viewpoint, somatic hotspot missense *FOXL2* mutations (c.402C>G; p.C134W) are found in approximately 95% of AGCTs, which are extremely rare in children, while the mutation is hardly ever reported in other SCSTs, including JGCT. Therefore, in cases where the differential includes AGCT and JGCT, demonstration of the presence or absence of a *FOXL2* mutation may be extremely useful.^{4,5} Patients with SCCOHT may have hypercalcaemia and do not exhibit features of precocious pseudopuberty or other hormonal manifestations. Immunohistochemistry is useful in distinguishing between JGCT and SCCOHT since the former is usually inhibin positive and the latter

Figure 1 Various morphological types of ovarian SCST. These may exhibit considerable morphological overlap and expert pathology review may be required for a correct diagnosis. (A) Ovarian JGCT with diffuse arrangement of cells and larger follicle-like structures containing basophilic material. (B) Ovarian adult granulosa cell tumour composed of diffuse and microfollicular arrangements of tumour cells with bland vesicular nuclei. (C) Ovarian well differentiated Sertoli-Leydig cell tumour composed of Sertoli cell tubules with intervening Leydig cells with abundant eosinophilic cytoplasm. (D) JGCT which is diffusely positive with inhibin; this is a useful marker of ovarian SCSTs but does not allow distinction between the various types. (E) Ovarian sex cord tumour with annular tubules showing characteristic 'punched-out' spaces containing hyaline material. (F) Ovarian Sertoli cell tumour composed of solid Sertoli cell tubules. JGCT, juvenile granulosa cell tumour; SCST, sex cord-stromal tumour.

negative. As discussed later, almost all SCCOHT lack expression of SMARCA4 (figure 2), while there is positive nuclear staining of JGCTs with this marker.

Cancer predisposition syndromes

JGCTs have been described in association with Ollier disease and Maffucci syndrome, subtypes of enchondromatosis syndromes (table 1). Tamimi and colleagues reported the first case of an ovarian JGCT in a 15-year-old girl with Ollier disease.⁶ Since then, 11 cases have been reported in the English literature.⁷ Ollier disease (OMIM #166000) and Maffucci syndrome (OMIM #614569) are skeletal disorders secondary to a dysplastic mesodermal process affecting the metaphyseal region of the short and long tubular bones. Although they are both types of non-spinal enchondromatosis, Maffucci syndrome includes soft tissue haemangiomas, while Ollier disease does not.⁸ They are considered non-hereditary disorders characterised by the presence of multiple enchondromas with asymmetric distribution with an estimated prevalence of 1/100 000.⁹ Somatic mutations in the *IDH1* and *IDH2* genes, classically affecting Arg132 of *IDH1* or Arg172 of *IDH2*, have been identified in enchondromas and haemangiomas in patients with Ollier disease and

Maffucci syndrome and have been linked to histone hypermethylation.^{8 10} A similar somatic mutation in these two genes has been suggested to explain the occurrence of JGCT, but this has yet to be confirmed.^{10 11}

Enchondromas that occur in Ollier disease and Maffucci syndrome become clinically apparent at a very young age and have the potential to transform into chondrosarcoma in up to 40% of patients.¹² Following enchondromas, haemangiomas and chondrosarcoma, JGCT is considered the most common tumour in patients with Ollier disease or Maffucci syndrome. Most patients have had a diagnosis of enchondromatosis prior to the occurrence of the JGCT. Interestingly, many reports have described the ovarian tumour to be located ipsilaterally to the predominant skeletal dysplasia.¹³ As the long bones of the skeleton and the gonads are both derived from the mesoderm, some authors have hypothesised that involvement of the ovary is a manifestation of a generalised mesodermal dysplasia process.¹³

Other CPSs have occasionally been reported in patients with JGCT. Plon and colleagues described a child with a JGCT who had a germline mutation in *PTEN* and *TP53*.¹⁴ *DICER1* somatic hotspot mutations have occasionally been identified in JGCTs, and two cases of JGCT have been associated with *DICER1*

Figure 2 (A) Small-cell carcinoma of the ovary of hypercalcaemic type composed of small round blue cells with scant cytoplasm and with follicle-like formations. (B) There is loss of nuclear staining with SMARCA4 (BRG1) with a positive internal control in the form of staining of endothelial cells.

Table 1 Features of paediatric ovarian tumours and their associated syndromes

Ovarian tumour	Common age of onset	Related CPS (gene)	% of cases associated with a CPS*	Features that increase the likelihood of a CPS	Other CPS-related tumours
Juvenile granulosa cell tumour	6–13	Ollier disease† Maffucci syndrome†	Low	P: Enchondromas (bony protuberances, skeletal angular deformities), haemangiomas F: N/A T: Unknown	Chondrosarcoma, brain tumours (glioma)
Sex cord tumour with annular tubules	10–30	Peutz-Jeghers syndrome (<i>STK11</i>) 25% <i>de novo</i>	High: 30%–35%	P: Younger age of onset, GI polyps, mucocutaneous hyperpigmented macules F: GI polyps, colorectal/gonadal/breast cancer, mucocutaneous hyperpigmented macules, large calcifying Sertoli tumours in males T: Bilateral, multifocal, small/microscopic tumours, microcalcifications	Mucinous ovarian and fallopian tube neoplasms and minimal deviation adenocarcinoma, GI polyps, colorectal cancer, cervical cancer, breast cancer, pancreatic carcinoma
Sertoli cell tumour	20–30	Peutz-Jeghers syndrome (<i>STK11</i>) 25% <i>de novo</i>	Low	P: Younger age of onset, GI polyps, mucocutaneous hyperpigmented macules F: GI polyps, colorectal/gonadal/breast cancer, mucocutaneous hyperpigmented macules, large calcifying Sertoli tumours in males T: Sertoli tumour of oxyphilic and lipid-rich subtypes	
Gonadoblastoma	15–19	<i>WT1</i> -related disorders—high <i>de novo</i> rate ► Frasier (<i>WT1</i> —intron 9 donor splice-site) ► Denys-Drash (<i>WT1</i> —missense mutations in exon 8 or 9) ► WAGR (11p13 deletion) Sex chromosome aneuploidy disorders	Moderate	P: Genitourinary tract structural malformations, aniridia, Wilms tumour, gonadal dysgenesis, renal parenchymal disease (FSGS or mesangial sclerosis) F: Wilms tumour, end stage renal failure/dialysis in young relative T: Bilateral tumours	Wilms tumour‡, early onset progressive nephropathy (Frasier=focal and segmental glomerular sclerosis; Denys-Drash=mesangial sclerosis)
Sertoli-Leydig cell tumour	15–30	<i>DICER1</i> syndrome (<i>DICER1</i>)	High: >50%	P+F: <i>DICER1</i> -associated neoplasms, younger age of onset T: Bilateral tumours	MNG, PPB, ERMS (cervical/ovarian), cystic nephroma, CBME, DTC, ASK, pineoblastoma, NCMH, PitB
SCCOHT	18–35	RTPS2 (<i>SMARCA4</i>) Low <i>de novo</i> rate	High: >30%	P: Young age of onset F: SCCOHT	Rhabdoid tumour (ATRT and extracranial MRT)

*Low: <1%, Moderate: 1%–25%, High: >25%.

†IDH1 and IDH2 somatic mosaic mutations described in enchondromas and haemangiomas of these patients.

‡Bilateral Wilms tumour and stromal-predominant histology increase the likelihood of a *WT1* germline variant.

ASK, anaplastic sarcoma of the kidney; ATRT, atypical teratoid rhabdoid tumour; CBME, ciliary body medulloepithelioma; CPS, cancer predisposition syndrome; DTC, differentiated thyroid carcinoma; ERMS, embryonal rhabdomyosarcoma; F, family; FSGS, focal segmental glomerular sclerosis; GI, gastrointestinal; MNG, multinodular goitre; MRT, malignant rhabdoid tumour; P, patient; PitB, pituitary blastoma; PPB, pleuropulmonary blastoma; RTPS2, rhabdoid predisposition syndrome type 2; SCCOHT, small cell carcinoma of the ovary of hypercalcaemic type.

syndrome,¹⁵ but a definitive link between JGCT and *DICER1* mutations requires a larger series of cases. As *DICER1* mutations are common in ovarian SLCT, it is possible that those JGCTs with the mutation represent misdiagnosed SLCTs; as discussed there may be morphological overlap between the two tumour types and JGCT-like areas may be seen in SLCTs.¹¹ The study of additional cases of JGCT associated with *DICER1* mutations, with expert pathological review to confirm the diagnosis, is required given these previous reports.¹⁵ Similar comments pertain to gynandroblastoma, a rare mixed ovarian SCST often exhibiting areas of both JGCT and SLCT; rarely these have been shown to contain *DICER1* mutations and it is possible that some of these represent misdiagnosed SLCTs with JGCT-like areas.

As only a handful of cases of JGCT have been reported in the context of enchondromatosis syndromes and the link between other CPSs is not established, we have very little evidence on which to base genetic counselling recommendations. However, physical examination in patients with JGCT should include evaluation for features of enchondromatosis (table 1). Equally, there are no standardised management strategies for ovarian tumour

surveillance in enchondromatosis syndromes. Although there are no consensus guidelines, we recommend that regular follow-up of growth and pubertal developmental be part of the surveillance for JGCTs in females with Ollier disease or Maffucci syndrome. As JGCTs are rare and characteristically benign, it seems reasonable not to incorporate specific ovarian imaging surveillance in enchondromatosis syndromes, unless clinically indicated.

Sertoli-Leydig cell tumours (SLCTs)

General aspects

SLCTs are an uncommon SCST, comprising 1%–2% of paediatric ovarian cancers.¹⁶ In a majority of cases, they are unilateral and confined to the ovary. They have been reported in females between the ages of 2 and 75, but most commonly occur in the second and third decades of life.¹⁷ SLCTs are composed of Sertoli and Leydig cells in varying proportions; according to the 2014 WHO Classification, they are categorised into well, moderately and poorly differentiated forms.¹⁸ Heterologous elements (including mucinous epithelium, rhabdomyoblastic and

Box Challenges in the pathological diagnosis of ovarian tumours in the context of CPS

- An individual pathologist may never encounter certain cancer predisposition syndrome (CPS)-related ovarian neoplasms (most of which are non-epithelial) throughout their career due to their rarity.
- Morphological overlap among ovarian sex cord-stromal tumours (SCSTs) may lead to 'picture-matching' and a potentially incorrect diagnosis. This can result in inappropriate management and a missed association with a CPS.
- Expert pathology review and specific immunohistochemical markers or molecular testing may be required for correct diagnoses, especially in the paediatric population.
- While immunohistochemical markers are useful in diagnosing an ovarian SCST, they are of little or no value in distinguishing between the morphological types.
- When uncommon tumours are assigned to a CPS, journal editors and reviewers must ensure, as far as possible, that the pathological description is adequate and accurate.

cartilaginous stromal elements, foci of carcinoid tumour) and/or a retiform pattern may be seen in moderately and poorly differentiated variants.¹⁸

Patients often present with hormonal manifestations, especially androgenic (leading to features of virilisation) and more uncommonly oestrogenic, including precocious puberty and menstrual abnormalities.¹⁷ Retiform tumours often develop at

a younger age and are less associated with endocrine manifestations.¹⁹ The degree of differentiation of SLCTs has been shown to correlate with the patient's prognosis, with well-differentiated forms almost always behaving in a benign fashion while poorly differentiated variants often exhibit malignant behaviour.¹⁷

Key differential diagnoses

SLCTs often result in diagnostic difficulties for pathologists in part because of their rarity and because they have a wide differential diagnosis (box). There may be considerable morphological overlap with other SCSTs and, as discussed, immunohistochemistry is of little or no value in distinguishing between the various SCSTs (figure 1D). However, immunohistochemistry is useful to distinguish SLCT from endometrioid carcinoma with which it may occasionally be confused. Similarly, retiform SLCTs may be confused morphologically with serous epithelial neoplasms but the latter occur at a much older age and the immunophenotype is different.

Cancer predisposition syndromes

SLCTs often manifest in the context of *DICER1* syndrome (OMIM #601200), which is characterised by germline mutations in the *DICER1* gene. In addition to SLCT, patients with this syndrome are at risk for developing very specific, typically rare paediatric neoplasms as well as more common neoplasms in adulthood (table 1, figure 3A).

Patients with *DICER1* syndrome typically have a loss of function germline mutation in *DICER1* that can occur anywhere along the gene, along with a somatic missense *DICER1* mutation

Figure 3 Pedigrees of families with manifestations of *DICER1* syndrome and *RTPS2*. (A) Family with *DICER1* syndrome-related manifestations. Affected relatives had a germline *DICER1* variant: c.1525C>T (p.Arg509X). (B) Two sisters with SCCOHT who inherited a germline deletion of the entire *SMARCA4* gene from their unaffected father. Black=affected, White=unaffected. +/- =wild type, +/- =heterozygous for pathogenic variant. MNG, multinodular goitre; *RTPS2*, rhabdoid predisposition syndrome type 2; SCCOHT, small cell carcinoma of the ovary of hypercalcaemic type; SLCT, Sertoli-Leydig cell tumour.

in trans, most often in the RNase IIIb 'hotspot' region.^{20 21} In non-hereditary cases of *DICER1*-related tumours, patients have two somatic mutations in *DICER1* with no germline mutation. SLCTs are by far the most common gynaecological manifestation of the *DICER1* syndrome and a recent study showed that 100% of moderately and poorly differentiated SLCTs contain either germline or somatic *DICER1* mutations.²² Conversely, this same study suggested that well-differentiated SLCTs are not associated with germline or somatic *DICER1* mutations.²² However, the number of well-differentiated SLCTs was small and currently we recommend that all patients with SLCT should be referred to a genetics service for consideration of *DICER1* testing. This study also showed that moderately and poorly differentiated SLCTs without *DICER1* mutations were misclassified neoplasms of some other tumour type, reinforcing the necessity for accurate pathology diagnosis (box).

In patients with SLCT, the presence of either bilateral tumours (a very rare phenomenon), a young age of onset or a personal or family history of a *DICER1*-related neoplasm should raise suspicion for a genetic cause.^{23 24} While the presence of a germline *DICER1* mutation does not currently have an impact on treatment or survival, it is important for clinical follow-up of the patient as well as for surveillance and education for other at-risk family members. For affected individuals and parents of younger girls with *DICER1* mutations, recognising the presenting clinical signs of SLCTs may be beneficial. Parents of patients with germline mutations may be unaffected due to either the low penetrance of *DICER1* mutations in the parent or a *de novo* variant in the patient. For patients with *DICER1*-related ovarian tumours, consensus recommendations from the 2016 American Association for Cancer Research Childhood Cancer Predisposition Workshop have recently been published.²⁵ For more information on *DICER1* syndrome, visit <http://www.dicer1syndrome.ca>.

Additionally, SLCTs have been seen in young women and children with Peutz-Jeghers syndrome (PJS; see next section for details on PJS).^{26 27} However, a definitive link between SLCT and PJS requires further study.

Sex cord tumour with annular tubules (SCTAT)

General aspects

Ovarian SCTAT is a rare neoplasm, representing approximately 1%–2% of ovarian SCSTs.^{28 29} They have been reported in females aged between 5 and 57 years, with slightly less than half presenting at ≤18 years.^{30 31} Most tumours are confined to the ovary, are rarely associated with hormonal manifestations and follow a benign course.^{30 31} While most of the time SCTAT is not associated with a genetic syndrome, in 30%–35% of cases it occurs in the setting of PJS. The non-syndromic cases are usually unilateral, large and symptomatic. They may exhibit malignant behaviour with spread beyond the ovary. Those associated with PJS typically occur in younger patients (mean age 28 years versus 34 years in non-syndromic cases) and are often an incidental microscopic finding in ovaries removed in females known to have this syndrome.³¹ They are typically small, bilateral and multiple and clinically benign, although a small proportion exhibit malignant behaviour with extraovarian spread.

Key differential diagnoses

The morphological features of SCTAT are characteristic and the diagnosis is often straightforward (figure 1E), although given the rarity of the neoplasm, many pathologists will never encounter a case.³¹ The differential diagnosis chiefly includes other SCSTs, especially AGCT, SCT and SLCT. However, the

rare gonadoblastoma, a mixed germ-cell and SCST may also enter into the differential diagnosis.³¹

Cancer predisposition syndromes

There is a well-recognised association between SCTAT and PJS.^{28 31} PJS is an autosomal dominant condition characterised by mucocutaneous melanocytic lesions, gastrointestinal hamartomatous polyps and the development of various benign and malignant neoplasms (table 1). The pigmented macules arise in the first few years of life in 90% of individuals; these may however fade with age. Approximately one-third of patients with PJS have symptoms related to gastrointestinal polyps by age 10 and two-thirds by age 20.³² The mean age of onset of ovarian tumours, particularly SCTAT (mean 28 years old), is lower than that of all other PJS-related cancers.³³ Patients with PJS may also develop other gynaecological neoplasms such as other ovarian SCSTs, non-HPV-related cervical adenocarcinomas (gastric-type) and mucinous neoplasms at various sites such as the ovary. Males with PJS can also develop testicular large-cell calcifying Sertoli cell tumours.

A germline mutation in the tumour suppressor gene *STK11* (also called *LKB1*) is the underlying cause of PJS in approximately 80%–90% of clinically affected families, without significant variation among racial and ethnic groups.³⁴ Almost half of affected individuals have no family history compatible with PJS and the *de novo* mutation rate is estimated to be 25%, demonstrating the value of genetic testing for diagnosis.³⁵ More than 300 causative variants in the *STK11* gene have been reported, the majority of which are loss of function, although missense variants and partial or whole gene deletions have been described.³⁶ Somatic loss of heterozygosity at 19p13.1 is seen in the SCTATs of patients with PJS.³⁷ A handful of studies have attempted to describe genotype-phenotype correlations with conflicting results.^{38–40}

The precise lifetime risk for a female carrier of an *STK11* germline mutation to develop a SCTAT is unknown but likely underestimated as they are often small and asymptomatic.⁴¹ The cumulative risk of developing an ovarian tumour in a *STK11* germline mutation carrier is approximately 20% between the age of 15 and 64 years, with SCTAT accounting for a majority of the ovarian tumours.^{31 42}

When a diagnosis of an ovarian SCTAT is made, clinicians should pay attention to aspects of the personal history, family history and tumour characteristics, which could suggest the presence of PJS (table 1). Considering the rarity of this ovarian tumour and its specific association with PJS, we recommend sending all children with SCTAT for a formal genetic evaluation and testing for a germline *STK11* mutation. Currently, no specific recommendations exist for surveillance for gonadal tumours in children with PJS. One group suggests starting yearly surveillance at age 25 with pelvic examination, pap smear and transvaginal ultrasound.³³ This surveillance is not specific to SCTAT, but is used for all gynaecological cancers. Nevertheless, a female carrier of PJS should be examined at least yearly with special attention paid to symptoms and signs which may suggest hormonal changes.⁴³

Sertoli cell tumours

General aspects

Sertoli cell tumours account for <5% of ovarian SCSTs and predominantly present in women of reproductive age (mean 30 years).⁴⁴ In a series of 54 patients (age range 2–76 years) reported by Oliva and colleagues, 14% of patients were prepubertal.⁴⁴ These tumours commonly result in hormonal

manifestations, especially oestrogenic and less commonly androgenic or progestogenic.^{19 44} Sertoli cell tumours (figure 1F) are most often benign neoplasms confined to the ovary and have an excellent prognosis with low reported rates of recurrence.⁴⁵ Rare lipid-rich and oxyphilic subtypes of Sertoli cell tumour have been reported.^{45 46}

Key differential diagnoses

Ovarian Sertoli cell tumours may have a wide differential diagnosis which can include other SCSTs (SLCT, AGCT, SCTATs), endometrioid carcinoma, carcinoid tumour and various metastatic adenocarcinomas.⁴⁴ A correct diagnosis and distinction from the other neoplasms in the differential may be facilitated by a panel of immunohistochemical markers.

Cancer predisposition syndromes

Sertoli cell tumours, particularly the lipid-rich and oxyphilic subtypes, have been described in children and young women with PJS.⁴⁷ In the series of Oliva and colleagues, 6/54 patients with Sertoli cell tumours were reported to have PJS, of which lipid-rich and oxyphilic subtypes were predominant.⁴⁴ In another report of 16 SCSTs from patients with PJS, four were lipid-rich and two were oxyphilic Sertoli cell tumours, with most of these SCSTs arising in the first two decades of life (range 4–30 years).²⁷ Conversely, in a study by Tavassoli and Norris of 28 patients with ovarian Sertoli cell tumour (age range 7–79 years), four had lipid-rich variants and none had signs of PJS.⁴⁵ In males with PJS, oestrogen-producing testicular Sertoli cell tumours have been reported.⁴⁸

When a diagnosis of a Sertoli cell tumour is made, clinicians should be aware of certain aspects of the personal history, family history and tumour characteristics (such as lipid-rich or oxyphilic subtypes) that raise the possibility of PJS (table 1). It seems reasonable to send a child with an ovarian Sertoli cell tumour for genetic counselling and testing for *STK11* mutations only if the clinician has a higher suspicion based on additional features.

GERM CELL TUMOURS

General aspects

Malignant germ cell tumours comprise 75% of ovarian neoplasms arising in the first 20 years of life and account for 15% of malignancies in adolescents aged 15–19 years old.⁴⁷

Ovarian germ cell tumours are a heterogeneous group of neoplasms arising from pluripotent primordial germ cells, including teratoma (mature and immature), choriocarcinoma, yolk sac tumour (YST; also called endodermal sinus tumour), dysgerminoma, embryonal carcinoma and mixed subtypes. Teratomas (the majority of which are mature) are the most common ovarian germ cell tumours, followed by dysgerminoma and YST.⁴⁹ Gonadoblastoma is a mixed germ cell-SCST with Y-chromosome material that characteristically develops in the context of gonadal dysgenesis. Although considered benign, gonadoblastomas have the potential to evolve into a dysgerminoma and exhibit malignant behaviour.^{50 51}

Ovarian germ cell tumours most frequently present with a palpable mass and abdominal pain, and approximately 10% can present with an acute abdomen as a result of ovarian torsion, haemorrhage or rupture.⁵² Certain subtypes may be associated with an elevated serum β HCG or alpha-fetoprotein (α FP).⁵³ Malignant germ cell tumours are highly curable, with 89%–98% survival rates.⁴⁹ Adverse prognostic factors include advanced tumour stage and elevated serum markers.^{54 55}

Key differential diagnoses

The differential diagnosis depends on the morphological subtype of germ cell tumour. Mature teratomas (dermoid cysts) are usually easily diagnosed. The differential diagnosis of some of the other morphological subtypes may include a wide range of non-germ cell neoplasms. A variety of immunohistochemical markers, including α FP, placental alkaline phosphatase, OCT3/4 and SALL4, may assist in diagnosis.

Cancer predisposition syndromes

Increasing evidence supports a genetic predisposition to the development of germ cell tumours. Genetic syndromes and multiple sex-chromosome aneuploidy syndromes leading to various degrees of gonadal dysgenesis have been consistently associated with germ cell tumour development, particularly but not limited to gonadoblastoma.

WT1-related disorders, most commonly Frasier syndrome and Denys-Drash syndrome (DDS), are described in association with ovarian gonadoblastoma. Both diseases are associated with steroid-resistant progressive nephropathy, gonadal tumours and male pseudohermaphroditism and therefore may easily be missed when the patient is phenotypically female.⁵⁶ The *WT1* gene is a tumour suppressor gene that encodes a zinc finger transcription factor involved in regulation of early gonadal and kidney development.^{57 58} It consists of 10 exons, with two regions of alternative splicing in exons 5 and 9. The final nucleotide of exon 9 codes for lysine, threonine and serine (KTS) and a correct ratio of KTS is necessary for the normal function of this gene.

Frasier syndrome is typically caused by a point mutation on the donor splice-site mutation in *WT1* on intron 9, leading to a decrease in +KTS isoforms.⁵⁹ It results in a slowly progressive glomerulopathy leading to nephrotic syndrome often in the first decade of life and typically resulting in renal failure in the second or third decade.^{60 61} These patients have gonadal dysgenesis with streak gonads, which are associated with a high risk of gonadoblastoma. The frequency of unilateral or bilateral gonadoblastoma in these patients is reported to be between 37% and 60%.^{60 62 63} Patients with Frasier syndrome who developed dysgerminoma have been described, some of these tumours having a gonadoblastoma component.^{63 64} Gonadal tumours are reported in 67% of type 1 (female XY) and 37.5% of type 2 (male XY), but not in type 3 (female XX) Frasier syndrome.⁶⁰

DDS results from a germline missense mutation in *WT1* exons 8 or 9 that code for zinc fingers 2 or 3, leading to abnormal production of the *WT1* protein.⁶⁵ Most cases of DDS are caused by one of two missense mutations located in exon 9: c.1180C>T (p.Arg394Trp) or c.1186G>A (p.Asp396Asn).^{65 66} This results in early-onset nephrotic syndrome and progression to renal failure, male pseudohermaphroditism and development of Wilms tumour.⁵⁶ Wilms tumours are the most frequent malignancies seen in patients with DDS. Unilateral or bilateral gonadoblastomas are described in patients with DDS, classically presenting in children between age 1.3 and 2.6 years.⁶⁷ In a series of 150 patients with DDS, the frequency of gonadoblastoma was reported to be 4%.⁵⁶ Gonadoblastoma, Wilms tumour and renal parenchymal disease tend to develop early, with an average age of presentation of 1.7 years for tumours and 1.4 years for the renal manifestations.⁵⁶

WAGR syndrome (Wilms tumour, Aniridia, Genitourinary anomalies and intellectual disability), caused by a partial deletion of chromosome 11p13, which includes the *PAX6* and *WT1* genes, has also been reported in cases of childhood ovarian

Table 2 Other CPS (non-sex chromosomal aneuploidy syndromes) associated with paediatric ovarian GCTs

CPS	Subtype of ovarian GCTs (age of onset in years)	Observed cases	First case
Cowden syndrome	Dysgerminoma (7)	1	Cho <i>et al</i> , 2008 ⁷⁷
Gorlin syndrome	Dysgerminoma (15)	1	Hoorens <i>et al</i> , 2016 ⁸⁴
BRCA1 germline mutations	Dysgerminoma (16)	1	Werness <i>et al</i> , 2000 ⁷⁸
Down syndrome	Dysgerminoma (11–17)	4	Gesundo <i>et al</i> , 1988 ⁷⁹ Satgé <i>et al</i> , 2006 ⁸⁰ Hasle <i>et al</i> , 2000 ⁸¹ Smucker <i>et al</i> , 1999 ⁸²
Noonan-like with CBL mutation	Mixed GCT (immature teratoma, dysgerminoma and YST) at 7 years, mature teratoma (14)	1	Hanson <i>et al</i> , 2014 ⁸³

CPS, cancer predisposition syndrome; GCT, granulosa cell tumour; YST, yolk sac tumour.

gonadoblastoma, although to a lesser extent than Frasier syndrome or DDS.⁶⁸

Gonadoblastoma has been reported in 10%–35% of patients with Turner syndrome with Y-chromosome material (45,X0/46,XY mosaicism).^{51 69 70} In a cohort of females with Turner syndrome, under 1% developed gonadoblastoma (only those with Y-chromosome material). This resulted in a cumulative risk of gonadoblastoma by age 25 years of 8%, which is likely an underestimate.⁷¹ Gonadoblastoma is seen in Turner syndrome and in the wide spectrum of other sex-chromosome aneuploidy syndromes associated to gonadal dysgenesis.

Following a diagnosis of an ovarian gonadoblastoma, a personal history of Wilms tumour, renal parenchymal disease, aniridia or an underlying urogenital malformation is highly suspicious for a *WT1*-related disorder (table 1). Given the rarity of familial *WT1* disorders, family history may not be the most helpful indicator.⁷² Short stature or delayed puberty in a female with a gonadoblastoma should also trigger investigations for a sex-chromosome aneuploidy syndrome, specifically Turner syndrome. The latest guideline for intersex disorders recommends gonadectomy in phenotypic females with XY karyotype who have DDS and Frasier syndromes.^{73 74} However, Ezaki and colleagues suggest that gonadectomy could be avoided in patients with Frasier syndrome type 3.⁶⁰ Gonadectomy is also recommended in Turner syndrome if Y-chromosome material is present.^{73 74}

For ovarian germ cell tumours other than gonadoblastoma, the association with CPSs is not as clear. Familial cases of ovarian germ cell tumours and familial clustering of benign teratomas and ovarian dermoid cysts have also been described, although no genes have yet been implicated.^{75 76} Paediatric case reports of ovarian germ cell tumours in the context of various syndromes have been published (table 2).^{77–84} Of note, reports describing ovarian germ cell tumours in patients with ataxia-telangiectasia (A-T) have been published.^{85 86} A-T, caused by biallelic mutations in the *ATM* gene, is associated with progressive cerebellar ataxia, oculocutaneous telangiectasia, immunodeficiency and cancer risk, especially haematological malignancies. Pathogenic variants in *ATM* result in DNA repair defects, making it essential to identify this syndrome, as patients can develop excessive toxicity to cancer therapy.

SMALL CELL CARCINOMA OF THE OVARY OF HYPERCALCAEMIC TYPE

General aspects

SCCOHT is an uncommon, but well-known, ovarian neoplasm, the histogenesis of which has been unknown until recently; it is included in the category of miscellaneous ovarian neoplasms in the 2014 WHO Classification. While uncommon, SCCOHT is the most frequent undifferentiated ovarian cancer presenting in women below the age of 40, with a mean age at diagnosis of 24 years.⁸⁷ It has been reported in females as young as 14 months,^{88 89} but most often arises in the second or third decade of life.⁸⁷ In two-thirds of cases, the patients have serum hypercalcaemia. SCCOHT is an extremely aggressive cancer, with 65% of cases recurring following primary therapy and long-term survival rates of 33%–55% for early stage and 0%–30% for advanced stage neoplasms.^{90 91} Due to the aggressive nature of the tumour, a correct diagnosis at presentation is crucial.

Key differential diagnoses

Establishing a diagnosis of SCCOHT may be difficult, as there is a broad differential diagnosis. The differential diagnosis may include a wide range of neoplasms, including AGCT, JGCT, germ cell tumours, endometrial stromal sarcoma, malignant melanoma, primary and metastatic small cell neuroendocrine carcinoma and a variety of small round blue cell tumours, which highlight the importance of expert pathology review for accurate diagnosis (box).^{87 92} While the tumour cells in SCCOHT usually have scant cytoplasm resulting in a small cell appearance, some cases contain tumour cells with abundant eosinophilic cytoplasm, often resulting in a large cell appearance, sometimes with a rhabdoid morphology. As discussed below, SCCOHT is caused by mutations in the chromatin remodelling gene *SMARCA4*.⁹⁰ These mutations are accompanied by loss of expression of the *SMARCA4* (BRG1) protein in 97% of cases, and immunostaining for *SMARCA4* has now been established as an extremely useful way to diagnose SCCOHT and distinguishes this entity from its mimics which almost always exhibit retention of nuclear immunoreactivity (figure 2).⁹³

Cancer predisposition syndromes

It has recently been established that SCCOHT is a monogenic disease and caused primarily by germline and somatic deleterious mutations in the chromatin remodelling gene *SMARCA4*, a member of the SWI/SNF chromatin remodelling complex.⁹⁰

Prior to the discovery of the association between *SMARCA4* and SCCOHT, it was found that germline mutations in *SMARCA4* can predispose patients to the development of rhabdoid tumours, including atypical teratoid/rhabdoid tumours, which are most often caused by mutations in another chromatin remodelling gene, *SMARCB1*.^{94 95} Germline mutations in *SMARCB1* and *SMARCA4* are associated with rhabdoid tumour predisposition syndrome types 1 and 2, respectively (RTPS1 and RTPS2); mutations were discovered to underlie the development of SCCOHT, and it was also recognised that these ovarian tumours are in fact morphologically very similar to rhabdoid tumours. Their similarity has led to the suggestion that SCCOHT is part of the rhabdoid tumour spectrum, and geneticists should now recognise that female carriers of pathogenic *SMARCA4* mutations are at risk for both rhabdoid tumours and SCCOHT.

While RTPS2-associated *SMARCA4* mutations are largely loss of function variants, a handful of missense variants have been described.⁹⁰ These variants have been found to occur across the length of the gene, with no predominant hotspot regions.⁹⁰

Missense variants in *SMARCA4* and other members of the SWI/SNF complex more often cause Coffin-Siris syndrome, a developmental disorder not associated with tumour development, rather than RTPS2.⁹⁶ Additionally, one case has been reported of a patient with a *de novo* *SMARCA4* nonsense variant and concomitant Coffin-Siris syndrome, microphthalmia and SSCOHT.⁹⁷

Although few familial cases have been described, studies have shown that up to 43% of patients with SSCOHT harbor a germline mutation in *SMARCA4*.⁹⁰ This often occurs in patients with no family history of SSCOHT or rhabdoid tumours, and in these cases, the pathogenic mutation is usually inherited from the patient's father.^{98,99} Penetrance of these mutations is still unknown.

Given the high incidence of *SMARCA4* germline mutations in patients with SSCOHT, we recommend that once the diagnosis is established, all patients should be referred to a genetics service and undergo genetic counselling. Patients diagnosed below the age of 20 years are highly likely to carry a germline mutation.⁹⁰ If a pathogenic mutation is found, all relevant relatives should undergo genetic counselling and testing for the familial variant. However, the unknown penetrance of these mutations and the young age of onset of this tumour makes it difficult to counsel mutation carriers and their families. Female carriers of truncating mutations are at risk for SSCOHT, and infant carriers of both genders may be at risk for rhabdoid tumours (table 1). As *SMARCA4*-mutated rhabdoid tumours have not been reported in patients older than 46 months, the development of these tumours in older carriers is unlikely.¹⁰⁰ However, the oldest woman to date diagnosed definitively with SSCOHT (showing loss of *SMARCA4* staining in her tumour) was 56 years old at diagnosis.⁹⁰ Further testing of affected and unaffected family members will hopefully elucidate the true penetrance and allow carriers to be more informed when making potentially life-altering decisions.

Currently there are no established preventive recommendations for female carriers. Bilateral oophorectomy would likely be an effective preventive measure,¹⁰¹ but without penetrance data, determining the optimal age to consider this option is difficult. Prophylactic oophorectomy may be considered by young females known to carry a germline *SMARCA4* mutation and has been performed in at least one adolescent carrier.⁹⁹ The efficacy of ovarian surveillance for female carriers is still undetermined, but until data are available, ovarian imaging is a reasonable option.

Although the familial incidence of SSCOHT, and RTPS2 in general, is low, it is important to note the high fraction caused by germline *SMARCA4* mutations and to recognise that even without a family history, the tumour may be hereditary if the patient has inherited a germline mutation from her father or acquired one *de novo* (figure 3B). Furthermore, it is important to note that infant carriers of both genders may be at risk for rhabdoid tumours in addition to SSCOHT.

CONCLUSION

Ovarian tumours in the paediatric population are not common, but in cases where they arise, consideration should be given to a possible underlying CPS, especially with a SCST. A thorough personal and family history should be collected as well as details on the tumour that may increase its likelihood of being the result of a germline mutation in a cancer predisposition gene. Although we have highlighted the most commonly known genes associated with these syndromes, novel sequencing techniques may uncover new genes and syndromes associated with uncommon ovarian tumours. Discovery of new gene-disease associations is outpacing clinical guidelines and physicians should always remain suspicious of a CPS following the

diagnosis of an uncommon/rare ovarian tumour in a paediatric patient.

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