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(RESEARCH ARTICLE)

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Recent updates in Ovarian Tumours: New recognized entities and molecular profiling according to the New 2020 WHO Classification of Female Genital Tumours

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Abstract

Among many gynaecological malignancies ovarian cancer is the most prominent and leading cause of female mortality worldwide. The fifth edition of the World Health Organization of tumours of the female genital tract divided Ovarian tumours into four categories: Epithelial/Surface, Germ Cell, Sex Cord- Stromal and Metastasis on the basis of distinct risk factors, pathogenesis, pattern of spread, genetic profiles, response to chemotherapy, and outcomes. Molecular profiling has enabled to identify peculiar alterations occurring among histologic subtypes. Taken all data together, advancement of technology and enabling the exploration of novel biomarkers that may be able to provide more accurate diagnosis and improve prognosis of the patients.

Keywords: Molecular profiling; Gynaecological malignacies; Ovarian tumours; Chemotherapy

1. Introduction

Ovarian cancer accounts for only 3% of cancer in women. However, it is the fifth most common cause of cancer death in women following lungs, breast, colorectal, and pancreatic cancers.[1] Ovarian cancer has an age-adjusted incidence of 12.5 per 100,000 women.[2] The incidence of Ovarian cancer and mortality rate increase with age. Most cases of ovarian cancer occur in women older than 50 years, but the diagnosis may be made at any age, including infancy. Ovarian tumours are divided into four categories: epithelial/ surface, representing almost 70% of cases, germ cell (10%), sex-cord stromal (15%) and metastasis (5%). Furthermore, each category divided into histologic subtypes. Epithelial origin tumours including high-grade and low-grade serous carcinoma, mucinous carcinoma, clear cell carcinoma, endometrioid carcinoma, brenner tumour, and mesenchymal tumours (endometrioid stromal sarcoma, leiomyoma, leiomyosarcoma, myxoma, and adenosarcoma). While germ cell tumours involve dysgerminoma, yolk sac tumour, embryonal carcinoma, choriocarcinoma, immature/mature teratoma and mixed germ cell tumour (includes struma ovarii, stromal carcinoid, cystic teratoma, and teratoma with malignant transformation). Lastly, sex-cord stromal tumours include fibroma, thecoma, Leydig cell tumour, granulosa cell tumour, Sertoli cell tumour, and gynandroblastoma. The New WHO classification divided and further subdivided ovarian tumours on the basis of distinct risk factors, different precursor lesions, clinical features, pathogenesis, histologic and molecular profiling, response to chemotherapy, and prognosis.[3-4] Recent studies has allowed to deepen the biology, the molecular alterations, the different sites of origin, opening the opportunity for a more personalized therapeutic approach and treatments with targeted drugs (e.g. PARP inhibitors).[5-7] In particular, massive molecular characterization studies have improved the comprehension of ovarian tumours genomics identifying peculiar alterations for each histologic subtype. Despite molecular pathology advancement, the fifth edition of the WHO classification of female genital tumours has similar diagnostic enitities as previous edition along with new histopathological, immunohistochemical, and molecular data.

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1.1. Epithelial/Surface tumour

Majorly, includes serous carcinoma (70-75%), endometrioid carcinoma (10%), clear cell carcinoma (6-10%), mucinous carcinoma (3-4%), and brenner tumour (<5%).

1.1.1. Serous Carcinoma

It is classified as High-grade serous carcinoma and Low-grade serous carcinoma. Firstly, High- grade serous carcinoma is the most common ovarian carcinoma (~70%), with higher incidence in white populations.[8] The mean age of patient is 65 years. Patients presenting symptoms are nonspecific and related to involvement of abdominopelvic organs. About 80% of patients present with FIGO stage III or IV disease. Elevated serum CA125 levels (>35 units/ml) are found in >90% of patients, but this is a nonspecific marker.[8] Women with deleterious germline BRCA1 or BRCA2 mutations have a 30-70% risk of developing HGSC by age of 70.[9-10] About 15% of cases are attributable to germline mutations in BRCA1 or BRCA2, and a small percentage (~1%) are associated with germline mutations in germline mutations in moderate penetrance gene such as RAD51C/D and BRIP1.

Microscopically, two histological types have described: classic type and SET (Solid, pseudoEndometrioid and Transitional) variants.[8] Both have similar immunoreactivity for WT1, p16, mutation-type labelled p53 and variable expression of ER, PR, CK7, CA125, and PAX8. CK20, CEA, HNF1B, and napsin A are typically negative in these tumours, while PTEN and ARID1A expression is retained. The molecular profiling identifies TP53 mutations in almost all tumours (96%). In addition to TP53 and BRCA1/2 mutations, other molecular characteristics included somatic copy-number alterations (SCNAs), which is correlated to genomic instability, CCNE1 amplification, and promoter methylation of 168 genes. Major sequencing techniques identified mutations in non-BRCA HR genes including ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAR51D.[11]

Secondly, low-grade serous carcinoma constitutes 3% of all ovarian carcinoma. Patients may be symptomatic or asymptomatic. Patients present over a wide age range (median: 43 years), approximately a decade younger than those with high-grade serous carcinoma.[8] Although LGSC has indolent growth, advanced disease is correlated with a worse prognosis because poorly responsive to conventional platinum-based chemotherapy. LGSC may exhibit KRAS, NRAS, BRAF, USP9X, and EIF1AX mutations. Loss of 9p and homogenous deletions of the CDKN2A/2B locus have also been reported.

Microscopically, it exhibits a variety of patterns, including small nests, glands, papillae or micropapillae, and inverted macropapillae- frequently free-floating within unlined clear spaces. In contrast to HGSC, mild to moderate nuclear atypia. Mitosis are usually <12 per 10 high power fields. Psammoma bodies are frequent. These tumours are frequently associated with a coexisting SBT as only differentiated by the presence of stromal invasion greater than microinvasion (invasive foci measuring >5 mm or 10 mm^2). LGSC are typically diffusely positive for CK7, PAX8, ER, and WT1; p16 expression is patchy and p53 exhibits wildtype immunoreactivity.[12] The most common molecular alterations include mutations of KRAS, NRAS, BRAF, USP9X, EIF1AX, and ERBB2 genes. BRAF or KRAS mutations occur in LGSC s in 30% and 35%, respectively, while ERBB2 mutation is uncommon (less than 5% of tumours). In addition, some authors have reported a better prognosis for LGSCs BRAF mutated than for those with KRAS mutations or with BRAF and KRAS wild-type. A recent comprehensive genomic study identified 47% of cases with mutations in key RAS/RAF pathway gene (KRAS, BRAF, and NRAS), as well as mutations in putative novel driver genes including USP9X (27%), MACF1 (11%), ARID1A (9%), NF2 (4%), DOTIL (6%), and ASH1L (4%).[13]

1.1.2. Endometrioid Carcinoma

It constitutes 10% of all ovarian carcinoma and these tumours may occur in the setting of Lynch syndrome. The median age of patients is 51 years (ranging from 26 to 87 years).[8] Most ECs are found at an early stage (FIGO stage I or II) at diagnosis. Most of ECs are frequently associated with endometriosis or contain areas of endometrioid adenofibroma and endometrioid borderline tumour. Atypical endometriosis represents the precursor lesion of about 40% of ECs.[14-16]

Microscopically, it resembles uterine endometrioid adenocarcinoma and its variants. Low grade EC shows variable architecture such as cribriform, villoglandular, papillary, or/and labyrinthine glands. While High grade ECs are poorly differentiated tumours characterized by solid growth, markedly atypical cells, and high mitotic activity. The so-called "confirmatory endometrioid features" are histologic characteristics reported in EC and include (i) metaplastic features (squamous, moral, hobnail, or mucinous) or other alterations in cellular phenotype (eosinophilic or secretory change); (ii) association with endometriosis, ovarian endometrioid adenofibroma or endometrioid borderline tumour; or (iii) presence of a synchronous uterine endometrioid neoplasm.[16] ECs show immunopositivity for PAX8, Vimentin, ER, PR

and nuclear expression of Beta- catenin. Unlike HGSC, ECs are usually negative or only focal positive for WT1, p53, and p16. High grade EC may show p53 mutation pattern staining.[12]

The most common molecular alteration in ovarian endometrioid carcinomas affect the WNT/Beta catenin signalling pathway (CTNNB1 mutations, 53%), the PI3K pathway (PIK3CA, 40%; PTEN, 17%), the MAPK pathway (KRAS, 33%), and the SWI/SNF complex (ARID1A, 30%).[17] Analogous to the molecular subtypes of endometrial endometrioid carcinoma defined by The Cancer Genome Atlas (TCGA), four molecular subtypes of ovarian endometrioid carcinoma have been proposed: hypermutated due to mismatch repair deficiency (~13%), ultramutated due to POLE exonuclease domain mutations (~5%), TP53-mutated (9-13%), and no specific molecular profile (NSMP;69-73%). Compared with endometrial carcinoma, ovarian EC has a similar frequency of Beta catenin mutations but a lower rate of MSI and PTEN alterations. CTNNB1 mutations occur in 38-50% of cases.[18] PTEN is a tumour suppressor gene located on chromosome 10q23.3 and is mutated in approximately 20% of ovarian EC.[19] Mutation in ARID1A (AT-rich interactive domain 1A gene), and loss of expression of the encoded protein BAF250a, occur in approximately 30% of EC but these are more frequent in CCC (50%).[20] The reported frequency of MSI in ovarian ECs ranges from 10-20%. Similar to endometrial carcinoma, MSI has been demonstrated in patients with Lynch syndrome/ hereditary non-polyposis colon cancer syndrome. These patients are characterized by an inherited germline mutation in the DNA mismatch repair (MMR) protein genes MLH1, PMS2, MSH2, or MSH6 ("first hit"), but EC develops only after the deletion or mutation of the second corresponding allele ("second hit").[21-22]

1.1.3. Clear Cell Carcinoma

CCC accounts 10% of ovarian carcinoma, with high prevalence in Asia (27% in Japan). The mean patient age is 56 years.[8] CCC are strongly associated with endometriosis, while a portion of tumours contains adenofibromatous and borderline areas. In some studies, MMR deficiency and/ or Lynch syndrome-associated CCCs have been correlated to an unexpectedly long survival, and this may reflect tumour immunogenicity with the potential for immunotherapy in such cases.

Microscopically, CCCs show three classical architectural patterns are described: papillary, tubulocystic, and solid. Three characteristic microscopic features for the diagnosis of CCC: (1) multiple complex papillae; (2) densely hyaline basement membrane material or mucoid stroma expanding the cores of the papillae; and (3) hyaline bodies.[16,23] CCC shows immunopositive expression of hepatocyte nuclear factor 1-beta, negative staining for WT1, ER, and PR expression, and wild-type pattern of p53 expression.[12]

About 40-50% of cases harbour loss-of-function mutation in ARID1A. ARID1A is a tumour suppressor and part of the SWI/SNF chromatin remodelling complex. PIK3CA mutations occur in 30-40% of ovarian CCCs and commonly coexist with ARID1A alterations. PTEN mutations and/or loss of heterozygosity have been described in 5-20% of tumours. While mutations in telomerase reverse transcriptase (TERT) promotor resulted in 15.9% ovarian CCC.[22] In contrast to endometrioid carcinoma, CTNNB1 (beta catenin) alterations and MSI are uncommon in CCCs. Of note, MMR deficient/Lynch syndrome-associated tumours are unexpectedly correlated with good prognosis even in advanced stages.[24]

1.1.4. Mucinous Carcinoma

It accounts 10-15% of all primary ovarian tumours and the vast majority (>80%) are benign or borderline tumours; mucinous carcinoma represents only 3-4% of ovarian carcinoma.[8] The median patient age is 55years. The origin is unknown. Although MC subgroup may derive from ovarian teratomas, in most cases no teratomatous component can be observed. They may be associated with pseudomyxoma peritonei.

Microscopically, it may exhibit two patterns of growth: (i) an expansile type without obvious stromal invasion but with back-to-back or complex malignant glands with minimal or absent stroma; and (ii) an infiltrative type, with obvious stromal invasion and frequently associated with a desmoplastic stromal reaction. The expansile growth pattern is associated with a more favourable prognosis than the infiltrative pattern.[25] MC shows diffuse and strong immunopositivity for CK7 and variable positive for CK20, CEA, and CDX2. CA19-9 is often diffusely positive; CA125, WT1, napsin A, vimentin, ER, and PR are usually negative. PAX8, usually focal and weak, is positive in a subset of tumours. P53 may show wildtype or mutation-type staining; p16 is usually negative or focally positive. Diffuse strong positivity for SATB2 can be seen in mucinous tumours associated with mature teratomas.

The most common molecular alterations are copy-number loss of CDKN2A (76%) and KRAS mutations (64%), both considered to be an early event because they have been identified in precursor lesions at similar frequencies. TP53 mutations occur in 64% of these tumours, a higher frequency than in mucinous borderline tumours. ERBB2 (HER2)

amplifications are detected in 15-26% of tumours and occur almost exclusively in a TP53-mutated background. KRAS mutations are almost mutually exclusive of HER2 amplification. Approximately 34% of MCs have neither HER2 amplification nor KRAS mutation, and these cases are associated with an increased risk of recurrence and poor prognosis compared with tumours with either molecular alterations. The mutations in RNF43, BRAF, PIK3CA, and ARID1A (8-12% of cases) were the next most frequent.[26]

1.1.5. Brenner Tumour

It accounts for approximately 5% of benign ovarian carcinoma. It shows bimodal age distribution of patients i.e. <30 years or/and >80 years.

Microscopically, it is composed of small oval to irregular nests of bland transitional/urothelial epithelium in dense fibrous stroma. Borderline BT resembles low-grade papillary urothelial neoplasms of the urothelial tract. Tumours with strong invasion, as defined by infiltrative nests with a desmoplastic stromal response, should be designated as malignant BT. Mucinous glandular elements and (more rarely) mucinous adenocarcinoma may coexist within the Brenner component. The absence of a benign or borderline Brenner component should raise the possibility of high-grade serous or endometrioid carcinoma with transitional cell-like differentiation. BT express immunopositivity for GATA3, CK7, p63, S100P, AR, uroplakin, and thrombomodulin, but they do not express (or only focally express) CK20. PAX8, WT1, ER, and PR are typically negative. P53 shows a wildtype immunoreactive pattern, and p16 can show loss of staining.

Disease-specific mutation are not known. Alterations in CDKN2A (the gene encoding p16INK4a) have been reported, resulting in loss of p16 staining by immunohistochemistry. KRAS and PIK3CA mutation as well as MDM2 amplification have been reported. But mutations in the TERT promoter or TP53 have not been found.[8]

1.2. Germ cell tumours

Ovarian GCT classified into three categories- primitive GCT, teratomas and monodermal and somatic-type tumours arising from dermoid cyst. Furthermore, primitive GCTs are subdivided into: Dysgerminoma, Yolk sac tumour, Embryonal carcinoma, Non-gestational choriocarcinoma ,and Mixed GCT (at least two malignant histologies); Teratomas are subdivided into: Mature teratoma, and Immature teratoma; and Monodermal and somatic-type tumours arising from dermoid cysts are subdivided into: Struma ovarii (benign and malignant), Ovarian carcinoid, Neuroectodermal type tumours, Monodermal cystic teratomas, and Somatic neoplasms arising from teratoma.

1.2.1. Dysgerminoma

It accounts for about 1% of all ovarian tumours. It arises in children and young women, as well as in some phenotypically female individuals with gonadal dysgenesis. Patients present with abdominal pain or an abdominal mass and elevated serum LDH. There is nonspecific elevation of serum alkaline phosphatase (ALP) and lactic dehydrogenase, and 5% of dysgerminoma secreate beta-HCG because they contain multinucleated syncytiotrophoblastic giant cells.[8]

Microscopically, uniform, large tumour cells are separated by fibrovascular septae which is almost infiltrated with chronic inflammatory cells, especially lymphocytes. It shows immunopositive expression for SALL4, OCT4, LIN28, NANOG, placental alkaline phosphatase (PLAP), CD117, D4-40, with c-KIT mutation being present in 33-50% of patients.[27-28]Cytokeratins may be focally positive. EMA, CD30, and glypican-3 are negative. Dysgerminomas have a favourable prognosis, with a ten-year survival of approximately 90%. Recurrence occurs in about 10% of cases, typically within 2 years of initial presentation. It is associated with KIT mutations (30-50% cases), and chromosomal gains of the 12p arm containing KRAS, occurring in up to 80% of patients with dysgerminoma. Overexpression of several genes has been described in dysgerminoma, including CASP8, CDH3, CXCL10, and IL6R and the pluripotency-related genes NANOG, POU5F1B, PLBD1, and PDPN.[29]

1.2.2. Yolk Sac Tumours

It accounts for 20% of malignant ovarian GCTs and mainly occur in women in their second and third decades of life. Patients present with abdominal pain, a palpable abdominal mass, or an acute abdomen secondary to ovarian torsion. Unlike dysgerminoma, serum AFP and CA-125 will be elevated in most patients.[30] Microscopically, it exhibits multiple patterns: most commonly a reticular/ microcystic (loose meshwork of cysts and tumour cells that have a signet-ring morphology); endodermal sinus (festoon) pattern (with tumour cells and schiller-duval bodies); and/ or other patterns such as solid, alveolar-glandular, parietal, papillary, polyvesicular vitelline, hepatoid, and myxomatous pattern.[8] It shows immunopositivity expression of SALL4, LIN28, AFP (often focal and weak), glypican-3, and ZBTB16, as well as CDX2 in the intestinal-type pattern, Hep Par-1 in the hepatoid pattern, and TTF1 in the foregut/respiratory pattern.

YSTs are aneuploid with characteristic copy number alterations, including chromosome 12p gain in approx. 60% of the tumours, but are not associated with specific recurrent mutations.[29,31] PIK3CA and AKT1 were amplified in 42% and 37% cases respectively.[31] Gene expression studies suggest that TGF-beta/ BMP and Wnt/ beta-catenin signaling pathways are activated in YSTs, but not in dysgerminomas.[32] The 5 year survival rates are >95% for stage I-II, 70% for stage III, and 50% for stage IV. YST coexisting with ovarian or endometrioid cancer has a worse prognosis.

1.2.3. Mixed Germ Cell Tumour

It is composed of more than one histological form and account for approx. 5% of malignant ovarian GCTs. Beside dysgerminoma and YST, other rare histologic subtypes such as embryonal carcinoma, choriocarcinoma, and polyembryoma cell types account for 5-10% of MOGCTs and have the worse prognosis. It exhibits a gain of 12p or isochromosome 12p. Embryonal carcinoma expresses CD30 in approx. 80% of cases, although expression may decrease after treatment with chemotherapy.[33-35] Choriocarcinoma shows alteration in Wnt/beta-catenin signaling pathway.

1.2.4. Immature Teratoma

Immature teratoma has comparable or higher incidence than dysgerminoma (30-35% of MOGCTs), usually presenting within the first three decades of life. Elevated serum AFP should prompt more-extensive sampling of the tumour to rule out YST, but tumours with hepatoid components may have elevated AFP. Histologically, variable amounts of immature tissues, mostly neuroectodermal tubules and rosettes, are admixed with ectodermal and endodermal tissues in varying maturation. It should not have foci of YST. If such foci are present, the case should be classified as mixed GCT but elevated serum levels of AFP, that should prompt additional sampling of the specimen to find a focus/component of YST, which would change the classification to mixed GCT. It shows immunopositive expression of SALL4, SOX2, AFP and glypican-3.[8]

Unlike other MOGCTs, Immature teratoma is typically diploid, and chromosome 12p gain and KIT/KRAS mutations are uncommon.[31] It also shows uncovered extensive loss of heterozygosity without recurring somatic mutations. Variants without known functional significance were detected in TP53, NF1, CTNBB1, and NOTCH2. While recurrent mutations were not common, variants of unknown significance in POLE, BRCA2 and ATM were detected.[36]

1.3. Malignant Sex Cord-Stromal Tumours (SCSTs)

SCSTs arise from the primitive sex cord and/or stromal cells of the gonads. It represents approx. 7% of all primary malignant ovarian tumours. It usually occurs in the first two to three decades of life, with the exception of adult granulosa cell tumours which are characterized by later onset with a peak incidence between 50 and 55 years of age. Patient may present with an adnexal mass, abdominal distention, and abdominal pain. Unlike epithelial and germ cell tumours, some SCSTs have clinical signs of hormonal production, including menstrual changes, precocious puberty, hirsutism, post-menopausal bleeding and/or virilization.[8]

It is classified into three categories: pure stromal tumours, pure sex cord tumours, and mixed sex cord stromal tumours. Furthermore, each categories are subdivided i.e. (i) pure stromal tumours include fibroma, thecoma, sclerosing stromal tumours, and other rare entities are fibrosarcoma, microcystic stromal tumour, leydig cell tumour, steroid cell tumour; (ii) pure sex cord tumours include adult granulosa cell tumour, juvenile granulosa cell tumour, and rare entities are Sertoli cell tumour; and (iii) mixed sex cord stromal tumours include Sertoli-leydig cell tumour.

2. Pure stromal tumour

2.1. Ovarian Fibroma

It accounts for 4% of all ovarian tumours. Fibroma occur in approximately 75% of female patients with naevoid basal cell carcinoma syndrome or basal cell nevoid syndrome (Gorlin syndrome); and Meigs syndrome (ascites and pleural effusion) occurs in a small proportion of cases. It may occur at any age; it most frequently arises in middle age (~48 years) and less commonly before the age of 30 years. These solid, typically benign, tumours arise from spindle shaped stromal cells that form collagen. Fibromas are commonly unilateral; however, bilateral cases may occur and may be associated with gorlin syndrome, a rare autosomal dominant hereditary disease. It affects multiple organ systems of the human body and is associated with an increased risk of developing several types of benign and malignant tumours. It may be immunoreactive for inhibin, calretinin, WT1, FOXL2, CD56, SF1, and hormone receptors. This syndrome is caused by a germline mutation in the human homolog of the PTCH1 gene and STK11, which are located on chromosome 9 (9q22.3) and chromosome 19 (19p13.3) respectively. Molecular cytogenetics analysis by fluorescence in situ hybridization has shown the presence of trisomy 12 in fibromas.[37]

2.2. Thecoma

Thecomas are uncommon, accounting for 0.5-1% of all ovarian tumours.[38] They occur at any age and can be seen in women under 30 years of age.[39] These tumours are hormonally active and consist of lipid laden stromal cells that may or may not be luteinized. Immunohistochemically, thecomas are typically positive for inhibin, calretinin, and other sex cord makers. Cytogenetics analysis of the thecoma has identified the presence of trisomies of chromosomes 12 and 4.[40] Trisomy 12 is the most frequent aberration in benign sex cord-stromal tumours, and it is suggested that trisomy 4 may be a later event in the tumorigenesis of thecomas.[40]

2.3. Sclerosing Stromal Tumour

It represents <5% of all sex cord-stromal tumours, and 70% are diagnosed in young women aged 14-29 years.[41] Microscopically, SST has pseudolobular appearance with cellular lobules that are composed of spindled and epithelioid cells, separated by a hypocellular oedematous, collagenous, or occasionally myxoid stroma. On immunostaining, SSTs show strong TFE3 expression, which is a transcription factor binding to the immunoglobulin heavy chain enhancer 3.[42] Sex cord markers such as inhibin and calretinin also show immunoreactivity. FISH studies on a small subset of tumours have reveal a subpopulation of tumour cells with trisomy 12. Recently, recurrent FHL2-GLI2 fusion genes have been demonstrated in 65% cases and other GLI2 rearrangements in an additional 15% of cases.[43]

2.4. Microcystic Stromal Tumour

MSTs are very rare; present in patients between the ages of 20 and 60.[44] Histologically, it exhibit a classic triad of microcysts, solid cellular zones, and fibrous stroma. Tumour cells are usually diffusely positive for beta-catenin, CD10, WT1, FOXL2, cyclin D1, and SF1, while inhibin, calretinin, ER, PR and EMA are typically negative.[8] The somatic exon 3 missense CTNNB1 mutation is a hallmark of most ovarian MSTs. The CTNNB1 gene encodes the beta-catenin protein, and this mutation leads to the loss of a phosphorylation site in the beta-catenin protein. Also, it may be associated with familial adenomatous polyposis, which is an autosomal dominant inherited disease caused by germline mutations of the adenomatous polyposis coli gene on chromosome 5 (q21-22).[45] A case study of the molecular analysis of MST by Zhang et al identified two missense mutations, one in exon 1 of the KRAS gene and the other in exon 15 of the adenomatous polyposis coli gene.[46]

3. Pure Sex Cord Tumour

3.1. Granulosa cell Tumour

GrCT accounts for up to 5% of overall ovarian cancers. There is an incidence of 0.61 cases per 100,000 women per year, accounting for around 2-5% of all ovarian cancers.[47-48] There are two types of GrCTs, which differ based on clinical signs and histopathological features: Adult GrCT and Juvenile GrCT.

3.1.1. Adult Granulosa Cell Tumour

It accounts for approximately 95% of all GrCTs, presents in perimenopausal and postmenopausal women, with a peak incidence in women aged 50-55 years.[49] Tumours may show a variety of architectural patterns: most common pattern is diffuse/ insular, trabecular, and microfollicular (call-exner bodies, hyalinized material). Less common patterns include gyriform and watered silk, macrofollicular, sarcomatoid, and pseudopapillary. Tumours are typically positive for FOXL2, calretinin, inhibin, and SF1. ER, pancytokeratin, CD99, and WT1 are frequently positive, and tumour can be positive for SMA, desmin, and CD10. PAX8, CK7, and EMA are typically negative.[8]

Several studies have reported that approximately 70-97% of adult GrCT carry a somatic c.402C>G missense point mutation in the FOXL2 gene.[50-52] This gene plays an essential role in ovarian development and differentiation. This make FOXL2a highly sensitive and relatively specific marker for adult GrCTs, as well as a useful diagnostic test for distinguishing between adult and juvenile GrCTs type and other sex cord-stromal tumours.[53] FOXL2 has been shown to interact directly with other genes involved in the pathogenesis of adult GrCTs, including CCND2, GATA4, and SMAD3.[54] Furthermore, FOXL2 expression is a potential prognostic marker for adult GrCTs, where patients with higher FOXL2 expression have a worse prognosis and worse overall rates of disease free survival than patients with negative or weak expression.[55] Several studies have investigated copy number changes in adult GrCTs and reported that gains in chromosomes 12 and 14 are observed in about 30% of cases, while chromosome 22 loss occurs in about 40% of cases.[56-58] A molecular study showed copy number changes in other genes, including LIMA1, RUNX1, and AKT1. These alterations may be involved in adult GrCT development and progression, along with the confirmed FOXL2 somatic mutation. Significant differences in gene expression have been identified between early (stage I) and advanced (stage III) adult GrCTs. Genes with the greatest fold change in expression included cytokine CXCL14 (chemokine C-X-C motif

ligand 14) and MFAP5 (microfibrillar associated protein 5 transcript variant 1). These two genes are prominently expressed in advanced stage adult GrCTs, while INSL3 (insulin-like 3 transcript variant 2) is highly expressed in stage I adult GrCTs.[53,59] Another study conducted by Alexiadis et al showed that a high frequency of promoter mutations in telomerase reverse transcriptase-124>T in adult GrCT is associated with more aggressive disease progression.[56] Using methylation specific PCR analysis, Xu et al study showed that the frequency of CDH13, DKK3, and FOXL2 promoter methylation was significantly higher in GrCT compared with follicular cyst tissue. Furthermore, immunostaining of EZH2, a histone H3K27 methyltransferase, showed positive expression in adult GrCT, while no expression in follicular cyst cases.[60]Another study of the methylation status of five gene promoters, including FHIT, FNACF, Cyclin D2, BRCA2, and RUNX3, in 25 GrCTS, showed that the methylation frequency was 28% for FHIT, 24% for FNACF, 12% for Cyclin D2, 4% for BRCA2, and 56% for RUNX3 genes.[66]Furthermore, the correlation of clinical features with promoter methylation status showed that overall promoter methylation was higher in higher stage tumours.[61] Another study performed by Dhillon et al assessed the promoter hypermethylation of different tumour suppressor genes, including MGMT, CDH1, RAR-beta, and SYK in 43 adult GrCTs.[62] They observed the hypermethylation of MGMT in 32%, CDH1 in 21%, RAR-beta in 19%, and SYK in 16% of tumours.[62]

3.1.2. Juvenile Granulosa Cell Tumour

It represents about 5% of all GrCTs. They are usually found in women younger than age 30, with a mean age of 13 years.[63] Patients may present with sign and symptoms related related to a pelvic mass, estrogenic manifestations including precocious pseudopuberty , irregular mensturation, or androgenic manifestation such as virilization or hirsutism.[64] Rare patients have Maffucci syndrome or Ollier disease. Tumours display a nodular or diffuse architecture, with scattered interspersed follicles of varying size that have irregular contours and often contain basophilic secretions. Occasionally, a pseudopapillary architecture is noted. Tumours usually express SF1, inhibin, calretinin, WT1, CD99, and CD56, and some express FOXL2 and EMA. Patients with tumours confined to the ovary have an excellent prognosis.[8]

Unlike adult GrCTs, juvenile GrCTs have either low or absent FOXL2 protein expression, therefore used to distinct between them. However, loss of FOXL2 leads to poor prognosis as the expression of FOXL2 is essential for establishing and maintaining granulosa cell identity in adult type.[65]Mutations in the GNAS gene, which encodes the stimulatory G protein, have been implicated in the development of juvenile GrCT.[66] A study conducted by Bessiere et al showed that >60% of cases bear in-frame duplications in the oncogene AKT1.[67]

3.2. Sertoli Cell Tumour

SCTs are uncommon, occur at any age (mean ~30 years). They are hormonally active in approx. 40-60% of cases; usually estrogenic but occasionally androgenic, and both. Tumours show variable patterns include trabecular, diffuse, alveolar, pseudopapillary, retiform, and rarely pseudoendometrioid and spindled. Lipid-rich and oxyphilic tumours may be associated with Peutz-Jeghers syndrome. Most of the tumours are immunoreactive for inhibin, SF1, calretinin, CD99, WT1, and broad spectrum cytokeratins. EMA, CK7, PAX8, GATA3, and chromogranin are negative. It harbours DICER1 mutations.[8] SCTs of the testis occur in patients who have peutz-jehgers syndrome, which is an autosomal dominant hereditary syndrome caused by germline mutations in the STK11/LKB1 gene.[68]

4. Mixed Sex Cord-Stromal Tumour

4.1. Sertoli-Leydig Cell Tumour

SLCTs are rare; they account <0.5% of all ovarian tumours. About 75% of SLCTs present in women under the age of 30. They are usually hormonally active, usually producing androgens, but sometimes producing estrogen. Approximately 80% of patients with ovarian SLETs present with virilizing manifestations. Most of these tumours are unilateral and confined to the ovary, and approx. 90% of cases are diagnosed at stage I. SLCTs are subdivided into well-differentiated, moderately differentiated, and poorly differentiated forms based on the degree of tubular differentiation of the Sertoli cell component (decreasing with increasing grade) and the quantity of primitive gonadal stroma (increasing with increasing grade). Leydig cells also decrease with increasing grade. Tumours are typically positive for vimentin and pancytokeratin, as well as for the sex cord markers alpha-inhibin, calretinin, SF1, WT1, and FOXL2. Leydig cells typically show either no or only minimal staining for FOXL2 and WT1, but they usually express alpha-inhibin and melan-A.[8]

There are three molecular subtypes of SLCT: (i) DICER1-mutant, seen in young age patients and associated with moderately/poorly differentiated tumour, retiform or heterologous elements; (ii) FOXL2 c.402C>G (p.Cys134Trp)-mutant, seen in postmenopausal patients and associated with moderately/poorly differentiated tumour, no retiform or heterologous elements; and (iii) DICER1/FOXL2-wild type, seen in intermediate patient age group and associated with well differentiated tumours, no retiform or heterologous elements. FOXL2 c.402>G (p.Cys134Trp) mutation has been

reported in 0-22% of tumours and is mutually exclusive with DICER1 mutations. Retiform differentiation and heterologous elements are highly predictive of DICER1 mutations. Both DICER1 and FOXL2 mutations have been reported only in moderately and poorly differentiated tumours.[8]

5. Conclusion

Ovarian cancer is a fatal gynecological illness that affects women of any age groups worldwide. Previously, due to lack of precise diagnostic biomarkers, the majority of women with ovarian cancer are diagnosed at an advanced stage, which reduces their survival rate. The need for an early detection and accurate diagnosis are essential in the current era of personalized therapy for a successful specific treatment. Advancements in our understanding of ovarian cancer biology that includes pathophysiology, histomorphology and respective genetic profile, has resulted in identification of a variety of molecular targets. In addition, advances in therapeutic technology have allowed significant insight into the molecular complexity and creating opportunities for diagnosis and prognosis that will significantly improve the overall survival rate and quality of life of patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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