should be incorporated into large-group trials of therapy for sex cord-stromal tumors.

**Prognosis**

The behavior of these tumors has not been easy to define because they may have a long clinical course with late recurrences and metastases. Prognosis is closely related to stage and degree of differentiation. In stage I Sertoli-Leydig cell tumors, only those of intermediate differentiation (11%), poor differentiation (59%) and those with heterologous elements (19%) have been clinically malignant. The retiform pattern also seems to be associated with more aggressive behavior. In contrast to granulosa cell tumors, recurrences of Sertoli-Leydig cell tumors usually occur early, in the first year after diagnosis.

Granulosa cell tumors are characterized by indolent growth with a significant capacity to recur many years after an apparent clinical cure.

Several pathological features have been evaluated as prognostic factors. Nuclear atypia, high mitotic rate, high Ki67 PI and the absence of Call-Exner bodies seem to be pathologic predictors of recurrence.

Other studies have investigated biological and molecular parameters by means of immunohistochemistry (c-myc, p21 -ras, c-erbB2, p53), but results have been inconsistent.

DNA ploidy, percent S-phase fraction, proliferative index and morphometric studies have been performed in series of granulosa cell tumors. Aneuploidy, S-phase fraction >10%, large nuclear area and nuclear perimeter seem to be adverse prognostic factors. Nevertheless, using these clinical, pathologic or biological parameters, it is difficult to predict early recurrences and impossible to predict late recurrences.

Trisomy of chromosome 12 has frequently been described in various neoplasms, particularly in tumors of the female genitourinary tract. Recently, this chromosomal abnormality has been found in a large proportion of sex cord-stromal tumors, including thecoma-fibromas, granulosa-carcinomas and Sertoli-Leydig cell tumors. The prognostic significance of trisomy 12 in these tumors is unknown.

Sex cord-stromal tumors of the ovary may present in a wide variety of morphological pictures, creating serious problems of differential diagnosis with other neoplasia. Recent advances have provided key markers to facilitate the correct diagnosis. The behavior of these tumors remains somewhat unpredictable, especially because of the lack of prognostic factors in early stage disease.

Further studies are needed to go deeper into the pathogenesis of these fascinating tumors.

**References**


**Neuroendocrine tumors of the ovary**

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Neuroendocrine tumors are a heterogeneous group of separate clinical-pathological entities, Which have a common characteristic, i.e., expression of endocrine differentiation potential. In order to diagnose endocrine differentiation within a tumor, we should first see the histological characteristics suggesting such differentiation and apply special studies only to confirm the suspicion. In the ovary, the term “neuroendocrine” relates mainly to the widely known carcinoids but it may also be applied to rare neuroendocrine carcinomas of non-small-cell type and small-cell carcinomas of pulmonary type, which have been described in recent years.

**Neuroendocrine carcinomas of non-small-cell type**

Neuroendocrine carcinomas of non-small-cell type are characterized by the presence of islands, sheets and trabeculae with little intervening stroma (organoid growth pattern) as well as by cellular homogeneity. Palisading of cells at the periphery of nests may be seen, particularly in low-grade tumors. Neuroendocrine carcinomas are higher grade than carcinoids. To date, nine such tumors have been reported and all developed in association with glandular mullerian-type component (seven mucinous-type tumors, one endometrioid carcinoma and one carcinosarcoma). Microscopically, the neuroendocrine component grew in the background of a surface-epithelial tumor but both components could be still recognized as separate. The tumor cells were medium-sized to large. Other cytological characteristics, i.e., the amount of cytoplasm, chromatin and...
nucleoli pattern were not consistent. In nearly all of the cases, the neuroendocrine tumor presented with moderate to marked atypia, high mitotic activity as well as extensive and/or single cell necrosis. The neuroendocrine differentiation was confirmed by the presence of two or more specific markers, i.e., argyrophilic and/or argentaffinic granules, chromogranin A and less frequently serotonin, synaptophysin and neuron specific enolase. Interestingly, most cells in the glandular components were also positive for chromogranin and serotonin.

The prognosis for neuroendocrine carcinomas of the ovary appears worse than that for typical surface epithelial carcinomas. In the series published by Eichhorn et al., three of three patients with available follow-up data died after 3, 8, and 36 months, despite early clinical stage in two cases. Patients reported by other authors died within 3 to 10 months of metastases to the liver, peritoneum or brain, despite postoperative chemotherapy.

Small-cell carcinomas of the pulmonary type

Primary ovarian small-cell carcinomas of the pulmonary type do not differ histologically from their counterparts in other organs. They are composed of small cells with scanty cytoplasm, with oval to spindle-shaped nuclei and inconspicuous nucleoli. The cells are arranged in closely packed sheets, islands and trabeculae. About 13 cases of this tumor type in the ovary have been reported. Eight of 11 tumors described by Eichhorn et al. had a component of müllerian tumor or epithelium, i.e., endometrioid carcinoma in four cases, squamous differentiation in one, and atypical mucinous epithelium in another; two small-cell carcinomas were associated with Brenner tumors. This suggests that, like non-small-cell neuroendocrine carcinomas, at least some primary ovarian small cell carcinomas of the pulmonary type develop in preexisting benign or malignant ovarian tumors. In the series published by Eichhorn et al., only two of nine tumors studied by histochemical and immunohistochemical techniques showed argyrophilia and positive chromogranin A staining. NSE was positive in six of nine tumors. These results are similar to those reported for pulmonary small cell carcinomas (reviewed by Eichhorn) but different from the neuroendocrine carcinomas of non-small-cell type. The prognosis for this tumor type is poor. Most patients with available follow-up data died within 1 year or had early recurrence.

Ovarian carcinoids

Ovarian carcinoids develop in pure form or in association with other tumors, mainly teratomas. They originate from endocrine cells, either of teratomatous, or possibly also of indigenous. There are four histological types of ovarian carcinoids: insular, trabecular, strumal and mucinous. Mucinous carcinoid and its special form, goblet cell carcinoid, are only exceptionally described as primary in the ovary. In the mucinous carcinoid, enterochromaffin cells are intimately admixed with mucin-filled neoplastic cells. In the goblet cell type, signet-ring cells (with no atypia or mitoses) create glands or solid structures similar to Brunner glands. One can also see cells with granular, eosinophilic cytoplasm, some of which are positive for serotonin. The nuclei are small, round or oval. Electron microscopy studies show either cells with secretory granules or goblet cells, or intermediate cells with both characteristics. Talerman also mentions a more atypical form of the ovarian mucinous carcinoid. The tumor is comparable to “argen- taff in cell carcinoma”, described by Soga et al. This carcinoid has adenocarcinoma architecture and is composed of glandular and solid structures with hyperchromatic nuclei and frequent mitoses. Most glandular and solid structures are argentaffinic and/or argyrophilic. Among enterochromaffin cells, one can also observe cells negative for these stainings but positive for mucicarmine. The material present in the glandular lumina is mucicarmolphic. Immuno- histochemistry reveals chromogranin A in many cells. Serotonin and gastrin may be present in some.

The mucinous type of ovarian carcinoid has a worse prognosis than other types. It behaves similarly to the mucinous carcinoid of the vermiform appendix; i.e., it spreads via the lymphatics and may extend beyond the ovary at the time of diagnosis.

References

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