Germ cell tumours of the ovary: selected topics

Esther Oliva

Robert H Young

Abstract

We discuss germ cell tumours of the ovary, beginning with dysgerminoma as it is the most common malignant germ cell tumour in this location. Issues in differential diagnosis are highlighted as this tumour is associated with an excellent outcome nowadays and can be confused with small cell carcinoma, clear cell carcinoma, and rarely other neoplasms.

The many patterns of yolk sac tumour are noted including the recently emphasized solid growth that may mimic dysgerminoma. Immunohistochemical stains are helpful in the diagnosis of both these primitive tumours, both being SALL4 positive and dysgerminoma expressing OCT4, D2-40 and c-KIT and yolk sac tumour having been recently reported to be GATA3 positive. Glypican-3 is also positive in yolk sac tumour but should be used with caution as it is often expressed in surface epithelial carcinomas, particularly clear cell carcinoma which can be in its differential. Where the fascinating polyembryoma should be placed in the classification of ovarian tumours is briefly considered.

In the teratoma family emphasis is placed on the gross differences between the mature cystic and immature forms. The most important categories of monodermal teratoma are then considered emphasizing their varied problems in differential diagnosis.

Keywords carcinoid; dysgerminoma; immature teratoma; mature cystic teratoma; neuroectodermal tumours; polyembryoma; struma ovarii; yolk sac tumour

Introduction

The goal of this essay is to focus primarily on some of the unusual clinical, gross, and microscopic aspects of germ cell tumours as well as problems in their differential diagnosis. Although morphology remains the bedrock in the evaluation of these often challenging tumours, immunohistochemistry has a role in this area. We will not cover the exceedingly rare embryonal carcinoma as its histopathology is no different from the familiar testicular counterpart. We will, however, discuss the rare polyembryoma, because of its intriguing morphologic features and even controversy as to where it best falls in the classification of gonadal tumours. Coverage primarily will focus on practical issues that will enable the pathologist to avoid errors in diagnosis which may potentially impact patient management adversely. Immunohistochemistry is also considered in some detail; molecular aspects are noted more sparingly but are mentioned when of interest. Space does not allow for extensive referencing so only selected references are provided; a more complete listing is available in the germ cell section of another essay we have written.[1] Endocrine aspects, often clinically intriguing, are also considered elsewhere.[2]

Esther Oliva *MD the James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA and the Department of Pathology, Harvard Medical School, Boston, USA. Conflicts of interest: none declared.*

Robert H Young *MD FRCPath the James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA and the Department of Pathology, Harvard Medical School, Boston, USA. Conflicts of interest: none declared.*

Primitive germ cell tumours

Dysgerminoma

This is the most common of the tumours in the primitive group. It presents most commonly as stage Ia disease in women who are <25 years and who typically have the usual symptoms associated with a sizeable adnexal mass but rarely patients may be virilized due to stromal luteinization in the tumour.[2] The latter in turn is usually due to stimulation by syncytiotrophoblast giant cells which can cause elevation of the serum HCG level. Rarely dysgerminoma causes paraneoplastic hypercalcaemia.[3] The dysgerminoma is the malignant tumour most often to arise out of a gonadoblastoma, the distinctive neoplasm that arises in the gonads of individuals, usually phenotypic females, with disorders of sexual development. This topic has been reviewed in detail elsewhere.[4]

This tumour has the most uniform sectioned surface among primitive germ cell tumours typically being lobulated and creamy white. It can be indistinguishable from two important tumours potentially in the differential on microscopic examination, small cell carcinoma of hypercalcemic type and malignant lymphoma. The latter is the one of the three most often bilateral (~half), dysgerminoma being 10% bilateral grossly and small cell carcinoma almost never. Areas of necrosis and/or haemorrhage may be seen. The latter is usually non-specific due to torsion, but exceptionally punctate foci of haemorrhage may reflect aggregates of syncytiotrophoblast giant cells on microscopic examination. Apart from the occasional association with gonadoblastoma, dysgerminoma is with rare exceptions seen only as part of a mixed neoplasm when it is associated with yolk sac tumour, the combination of those two neoplasms representing one of the commonest among primitive mixed germ cell tumours of the ovary.

The usual microscopic appearance of dysgerminoma is relatively straightforward, particularly when adequately fixed, a diffuse growth of tumour cells with a septal framework associated with a lymphocyte-rich inflammatory infiltrate occasionally containing few plasma cells (the latter not conspicuous) that may spread out into the cellular areas is its hallmark (Figure 1). The stroma ranges from barely perceptible to thin or thick collagen bands that are occasionally edematous or myxoid. Depending on the amount of the stromal compartment, various other patterns may result ranging from large aggregates to, more typically small nests and a rather uniform so-called alveolar growth. Rarely, the cells form solid or hollow tubules or surround spaces that may be small or large and follicle-like or can grow in cords (Figure 2) or even single cells (Figure 3).

The neoplastic cells are large and rounded with discrete cell membranes, clear to occasionally eosinophilic cytoplasm, and a central, large primitive nucleus with coarse chromatin and one or more prominent nucleoli (Figure 4). Dr. Scully referred to the nuclei as being "squared off" and emphasized the helpful nature

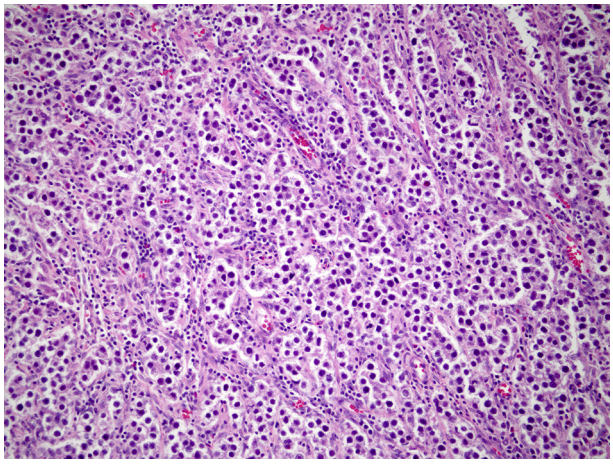

Figure 1 Dysgerminoma. The tumour cells grow in nests separated by delicate fibrous septa associated with a lymphocytic infiltrate.

of this finding including at the time of frozen section. The tumour cells are particularly prone to morphologic variations that are likely related to suboptimal fixation. These include loss of cohesion, lack of well-preserved cell membranes, eosinophilic cytoplasm, and rarely, signet-ring-like cells. Syncytiotrophoblast cells are seen in about 3% of these tumours.[5] Poorly formed granulomas, rarely sarcoid-like, occur in 20% of tumours and Langhans-type giant cells may be present.

Most dysgerminomas are PLAP positive, but this is not a very specific marker as it is expressed in other germ cell tumours[6] as well as surface epithelial tumours.[7] Most helpful markers include OCT4 (nuclear) (Figure 5),[8,9] D2-40 (podoplanin) (membranous),[10] and CD117 (c-kit) (membranous).[5] They also express LIN28[11] and like most other germ cell tumours they are SALL4 positive. They may express AE1/3-Cam5.2 to variable extent (<50% of cells) and very rarely CK7, but they are negative for EMA, high-molecular-weight keratin, and CD30.[12] These tumours have also recently been shown to display chromosome 12p abnormalities including isochromosome 12p and 12p overrepresentation and c-kit mutations as well as amplifications.[12,13]

It is important to separate dysgerminoma from other tumours in the differential diagnosis as the former have an excellent prognosis even if metastatic with modern therapeutic approaches.

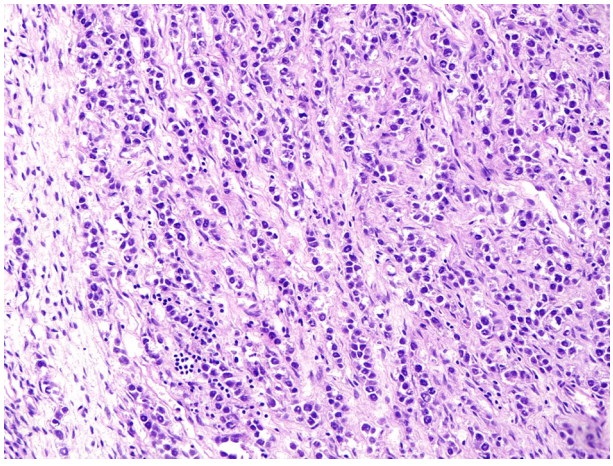

Figure 2 Dysgerminoma. The tumour cells grow in cords.

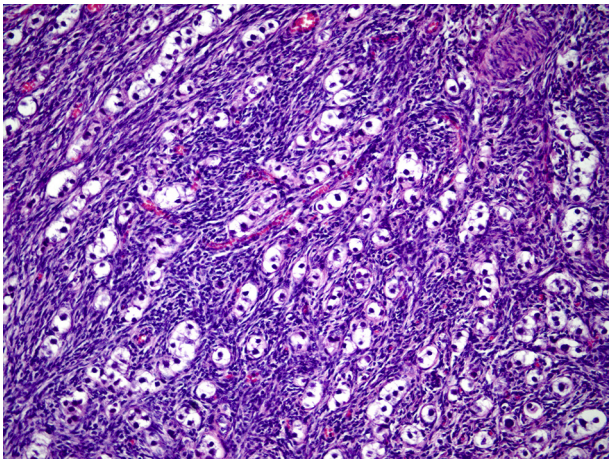

Figure 3 Dysgerminoma. An unusual pattern in which small aggregates or single cells infiltrate the ovarian stroma.

Small cell carcinoma, hypercalcemic type is an important entity to be aware of as the similar age range and gross appearance, the occasional association of hypercalcaemia and the presence of follicle-like spaces and small shrunken cells in some dysgerminomas may result in diagnostic problems. The diagnosis of dysgerminoma rests on finding foci with characteristic patterns and cytology and, if needed, immunohistochemistry. Follicle-like spaces are much more common in small cell carcinoma and a content of large cells with eosinophilic cytoplasm (often with a rhabdoid appearance) is rarely mimicked by the eosinophilic cells of dysgerminoma.[14,15] Occasionally dysgerminoma is confused with undifferentiated carcinoma but the latter is usually seen in older patients. That clinical difference can be important to reflect on if the diagnosis of undifferentiated carcinoma (non-small cell carcinoma type) is entertained in a young female. The possibility of a suboptimally preserved dysgerminoma should be considered and appropriate immunohistochemical stains performed. Also a poorly preserved dysgerminoma might lead malignant lymphoma to enter the differential diagnosis as may its gross appearance although architectural and particularly cytologic differences between dysgerminoma and any form of lymphoma are relatively overt, including ALK positive large B cell lymphoma,[16] possibly the most problematic in the differential.

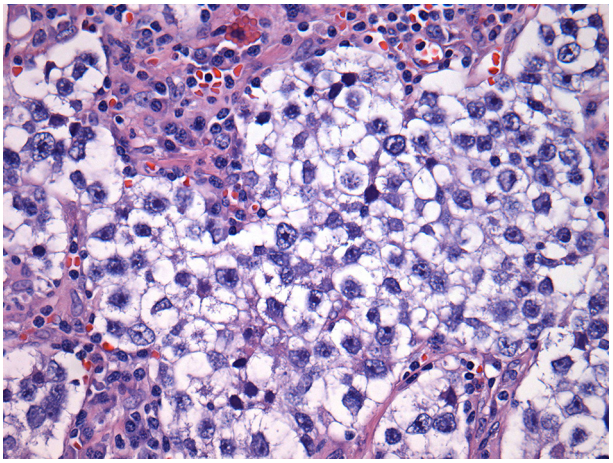

Figure 4 Dysgerminoma. Cells show typically abundant clear cytoplasm, large nuclei with “squared off” borders and prominent nucleoli.