Ovarian borderline tumours: a review with comparison of serous and mucinous types

W Glenn McCluggage

Abstract

Ovarian borderline tumours are relatively uncommon but not rare neoplasms. A large majority are of serous or mucinous type with other morphological variants being much more uncommon. In this review, the clinicopathological features of ovarian borderline tumours are discussed, concentrating on serous and mucinous neoplasms. Other morphological types are briefly discussed. A comparison is made between serous and mucinous borderline tumours which exhibit marked differences with regards to incidence of bilaterality, surface involvement, extraovarian spread, lymph node involvement, risk of malignant progression and prognosis. It has been suggested that the category of borderline tumour be abandoned for both serous and mucinous neoplasms but this terminology is useful for both types but for different reasons, namely the significant risk of extraovarian disease in serous borderline tumours and the large size and heterogeneity of mucinous borderline tumours which can result in an invasive focus being undetected by the pathologist.

Keywords mucinous borderline tumour; ovary; pathology; serous borderline tumour

Introduction

Ovarian borderline tumours were first described in 1929 when the term semi-malignant was used.[1] The preferred and most commonly used term and that used by the World Health Organization (WHO) is borderline tumour, an acceptable synonym being atypical proliferative tumour.[2] The terms tumour of borderline malignancy, cystadenoma of borderline malignancy and tumour of low malignant potential are not recommended. The most commonly used definition of a borderline tumour is "a noninvasive tumour that displays greater epithelial proliferation and cytologic atypia than benign tumours but less than carcinoma".[2] However, in many ways this is a less than adequate definition and using modern diagnostic pathological criteria, carcinoma may be diagnosed in some cases on the basis of architectural complexity and in the absence of overt destructive stromal invasion (discussed later).

Ovarian borderline tumours occur over a wide age range and not uncommonly affect young women where preservation of fertility may be an issue. The two most common morphological types are serous and mucinous, both of which are extensively discussed in this review. A comparison is made between serous and mucinous borderline tumours since these exhibit marked differences with regards to various clinicopathological parameters (Table 1). An argument is made for retention of the borderline terminology for both serous and mucinous neoplasms.[3–8] Mucinous borderline tumours comprise two distinct types, a much more common intestinal (gastrointestinal, enteric or non-specific) type and an uncommon Mullerian (endocervical) type; the latter has been renamed seromucinous borderline tumour in the revised 2014 WHO Classification.[2] Borderline tumours of endometrioid, clear cell and Brenner type are rare and are briefly covered.

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Histogenesis of serous and mucinous borderline tumours

Serous borderline tumours arise in most cases from a serous cystadenoma. Serous cystadenomas and serous borderline tumours are the precursor lesions of low grade serous carcinoma which are associated with KRAS or BRAF mutation in approximately two–thirds of cases.[9–15] These mutations occur early in the evolution of low-grade serous carcinoma since they can also be demonstrated in borderline and benign areas within the same tumour. KRAS and BRAF mutations appear mutually exclusive; in other words, one but not both may be present in a particular neoplasm. Low-grade serous carcinomas and serous borderline tumours are not associated with Tp53 mutation or other Tp53 abnormalities that are ubiquitous in high-grade serous carcinomas.[16,17] High-grade serous carcinomas are not, except in occasional cases, associated with KRAS or BRAF mutation. In contrast to high-grade serous carcinomas, serous borderline tumours and low-grade serous carcinomas are not associated with BRCA1/BRCA2 mutation or other BRCA abnormalities.

Similar to low-grade serous carcinomas and serous borderline tumours, ovarian mucinous tumours of intestinal type commonly exhibit KRAS mutations and identical mutations have been demonstrated in benign, borderline and malignant areas within the same neoplasm.[18] This suggests that KRAS mutation is an early event in the evolution of these tumours.[18] Unlike low-grade serous carcinomas, BRAF mutations are not a feature of ovarian mucinous neoplasms of intestinal type.

Occasional ovarian mucinous tumours of intestinal type, including some with a borderline morphology, arise within a teratoma which may have been obliterated and overgrown by the mucinous neoplasm (see section on **Histological Features of Intestinal Type Mucinous Borderline Tumours**). More uncommonly, mucinous tumours, including borderline neoplasms, may be associated with and arise within a Brenner tumour.

Pathological features of serous and mucinous borderline tumours

Gross features

Grossly, most serous borderline tumours are partly cystic and partly solid and the size is variable. They often comprise a unilocular cyst, although some are multiloculated. There is often an admixture of benign and borderline areas, the former in the form of thin walled cysts without papillary areas, although "thickenings" may be present which histologically correspond to areas of serous cystadenofibroma. The areas of borderline tumour are usually grossly apparent in the form of friable polypoid or papillary growths/excrescences which may project into otherwise smooth walled cysts (endophytic growth pattern) or from the surface of the ovary (exophytic growth pattern) (Figure 1). The pathologist should preferentially sample such

Comparison of pathological features of serous borderline tumours and mucinous borderline tumours of intestinal type

	Serous borderline	Mucinous borderline of intestinal type
Laterality	Approximately one third bilateral	Almost always unilateral
Capsule	May be friable papillary excrescences	Usually smooth
Locules	Often unilocular with internal papillary projections	Multiloculated
Intraepithelial carcinoma	Not applicable; in the presence of severe nuclear atypia, a diagnosis of high grade serous carcinoma is made	Yes — in presence of severe nuclear atypia
Microinvasion	Yes	Yes
Mural nodules	Extremely rare	Sometimes occur
Extraovarian implants	Yes	No
Lymph node involvement	Yes	No
Molecular events	KRAS and BRAF mutations	KRAS mutations

Table 1

polypoid/papillary elements. The borderline areas may make up a small percentage of the neoplasm or be extensive and in the latter case, the gross appearances may be extremely suggestive of a malignant neoplasm. Those uncommon borderline tumours with an adenofibromatous pattern have a more solid fibromatous appearance. Serous borderline tumours are bilateral in approximately one third of cases.

Intestinal type mucinous borderline tumours (by far the most common variant of mucinous borderline tumour) are almost always unilateral and are typically quite large, often in the region of 20 cm or greater, although the size is variable. These neoplasms are only rarely bilateral (there is no tendency for bilaterality) and with bilateral ovarian mucinous "borderline" neoplasms of intestinal type, a secondary with a pronounced "maturation phenomenon" should be considered and other features of metastasis looked for.[19,20] The capsular surface is usually smooth and surface involvement is unusual. On sectioning, there are usually multiple locules filled with thick tenacious mucoid material. Solid areas and areas of necrosis may be present and these should be preferentially sampled by the pathologist.

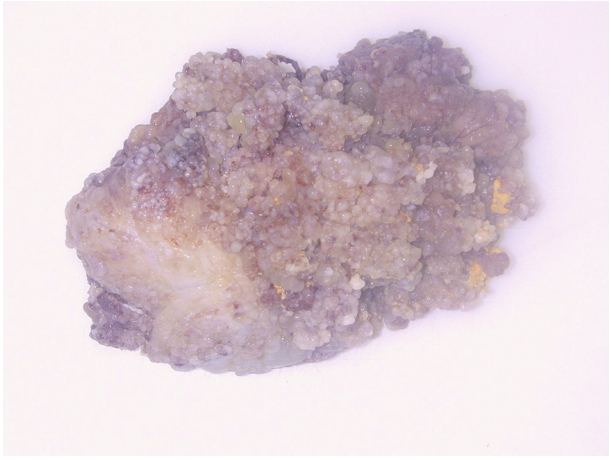

Figure 1 Gross photograph of serous borderline tumour with exophytic papillary excrescences.

Histological features of serous borderline tumours

Most serous borderline tumours are characterised by papillary fibrous or oedematous stromal cores covered by proliferating stratified epithelial cells. A hierarchical branching pattern characterised by papillae that branch from large to progressively smaller and terminating in detached tufts of epithelial cells is typical (Figure 2). There is usually an admixture of cell types with ciliated columnar and non-ciliated cells and a proportion of the cells often have abundant eosinophilic cytoplasm, sometimes with a hobnail appearance; this is more pronounced in serous borderline tumours in pregnancy. The epithelial cells exhibit mild or at the most moderate nuclear atypia. Psammoma bodies are commonly present. Mitoses are usually present but not numerous. In the presence of obvious and widespread high grade nuclear atypia, high grade serous carcinoma is diagnosed, even in the absence of obvious stromal invasion. As discussed, the epithelial proliferation in most serous borderline tumours is hierarchical, in contrast to the non-hierarchical pattern characteristic of the micropapillary variant of serous borderline tumour (discussed later). The borderline foci usually coexist with areas of benign serous cystadenoma and may project into cysts or from the ovarian surface. Areas of infarction of the papillae may be present, especially at the tips but sometimes involving much of the papillae. Uncommonly, serous borderline tumours exhibit an adenofibromatous growth pattern with proliferating serous type epithelium within a fibrous stroma. Small microscopic foci of epithelial proliferation are present in some serous cystadenomas and a descriptive report is recommended in such cases; for example, the term "focal epithelial proliferation insufficient for a diagnosis of serous borderline tumour" could be applied. Although there is no evidence base, it has been suggested that 10% of the neoplasm should exhibit proliferation and tufting for a diagnosis of serous borderline tumour.[4,8] However, if there are features of a "well-developed" serous borderline tumour with significant epithelial proliferation and tufting, I would make a diagnosis of serous borderline tumour, even if the epithelial proliferation involves less than 10% of the neoplasm.

Using the WHO definition, stromal invasion is absent in a serous borderline tumour and conversely destructive stromal