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EDITORIAL

High grade serous intraepithelial carcinoma arising in a benign ovarian serous cyst – a bridge too far?

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In 1973, our understanding of the nature of ovarian cancer was crystallised in the first series of the World Health Organization (WHO) *Histological Typing of Ovarian Tumours*[1] and was founded on three false premises. Firstly, as their cellular differentiation frequently recapitulated epithelial types found elsewhere in the female genito-urinary tract, they were regarded as a loosely related group of malignant tumours with similar or shared precursor lesions, clinicopathological correlates, behavioural patterns and outcomes that were predominantly dependant on stage and grade alone. Secondly, it was accepted that they represented the malignant end of a biological continuum which could, in each case, be divided into benign, proliferating (borderline) and frankly malignant variants. Thirdly, by circular logic, it was agreed that they were definitionally ovarian in origin, derived from native or acquired cellular elements in the ovaries, and with the capacity to spread only from these primary sites.

The passage of 40 years and publication of detailed clinicopathological studies have undermined these tenets, and stressed profound differences between the various histological subtypes, which are no longer regarded as simply variants within a single neoplastic disease process, but very much a heterogeneous mix of different tumours, some (mucinous) not even genitourinary in appearance. The long-held concept of a progressive biological evolution from benign, through borderline, to frankly malignant disease is also under challenge, except for a restricted minority of 'ovarian' cancer cases and the original *raison d'être* for the borderline subcategory remains tenuous at best. This has led the Johns Hopkins University group and others to propose an elegant dualistic model for ovarian carcinogenesis:[2,3] one less frequently encountered (Type I), associated with an adenoma-carcinoma sequence and generally low grade and low stage at presentation; and a second, much more commonly occurring (Type II), which is typically high stage and high grade at presentation and without accompanying benign or borderline precursor lesions. Finally, the article of faith that they are intrinsically ovarian in origin—and underpinning profligate attempts at screening for 'early' stage disease—has been replaced by an appreciation that the most commonly occurring subtype (high grade serous carcinomas) which account for 90% of ovarian cancer deaths,[4] very frequently, if not almost entirely, arise ultimately from serous tubal intraepithelial carcinoma (STIC) lesions in the lateral extremity of the fallopian tubes, i.e., are not ovarian at all. This sobering observation was initially highlighted around the turn of the century by groups investigating women at genetic risk of developing ovarian cancer,[5–11] although the association had been alluded to some 20 years previously.[12] Perhaps even more provocative, if less astounding, is the postulated origin of benign and proliferating (borderline) serous ovarian tumours, and perhaps even peritoneal and nodal endosalpingiosis, from benign epithelial lesions in the fallopian tube,[13] and spread transcoelomically or by lymphatics.[14–16] One might likewise claim that those ovarian cancers that arise in ovarian endometriosis are ultimately derived from tissue originating in the native endometrium and also, therefore, are not 'ovarian'.

With particular reference to serous tumours, the dualistic model[3] holds that, on the one hand, the Type I lesions include benign and proliferating (borderline) serous tumours and possibly arising from benign epithelial proliferations in the fallopian tubes which implant in the ovaries and elsewhere and, through a slow and fairly infrequent process, may progress in some women to low grade serous carcinoma (LGSC). They are genetically stable and are characterised by specific mutations including *KRAS*, *BRAF*, *ERBB2*, *PTEN* and *PIK3CA* but rarely *TP53*. Type II serous carcinomas, on the other hand, are the much more commonly encountered high grade and high stage carcinomas and are currently thought to derive from STIC lesions of the tubal fimbria. They are genetically unstable with a high frequency of *TP53* mutations and only rarely do they exhibit mutations typical of the Type I lesions. What then of the rarely encountered ovarian serous tumour that focally shares features of both Type I and Type II ovarian serous neoplasia? Is this a bridge across the great divide of the dualistic model—the exception that proves the rule—and how might it sit with the 'current' tubal origin of high grade serous carcinoma (HGSC) in general?

These thoughts were prompted by recently encountering just such an example: an asymptomatic ovarian cyst in an elderly patient, in which the luminal papillary excrescences were covered mostly by simple, columnar, ciliated epithelium, typical of serous differentiation (Fig. 1A,B). Also noted were several discrete foci of epithelial proliferation that emerged abruptly from the benign epithelium (Fig. 1A–D) mostly within the polypoid excrescences and in multiple sections. There was no transition via proliferating

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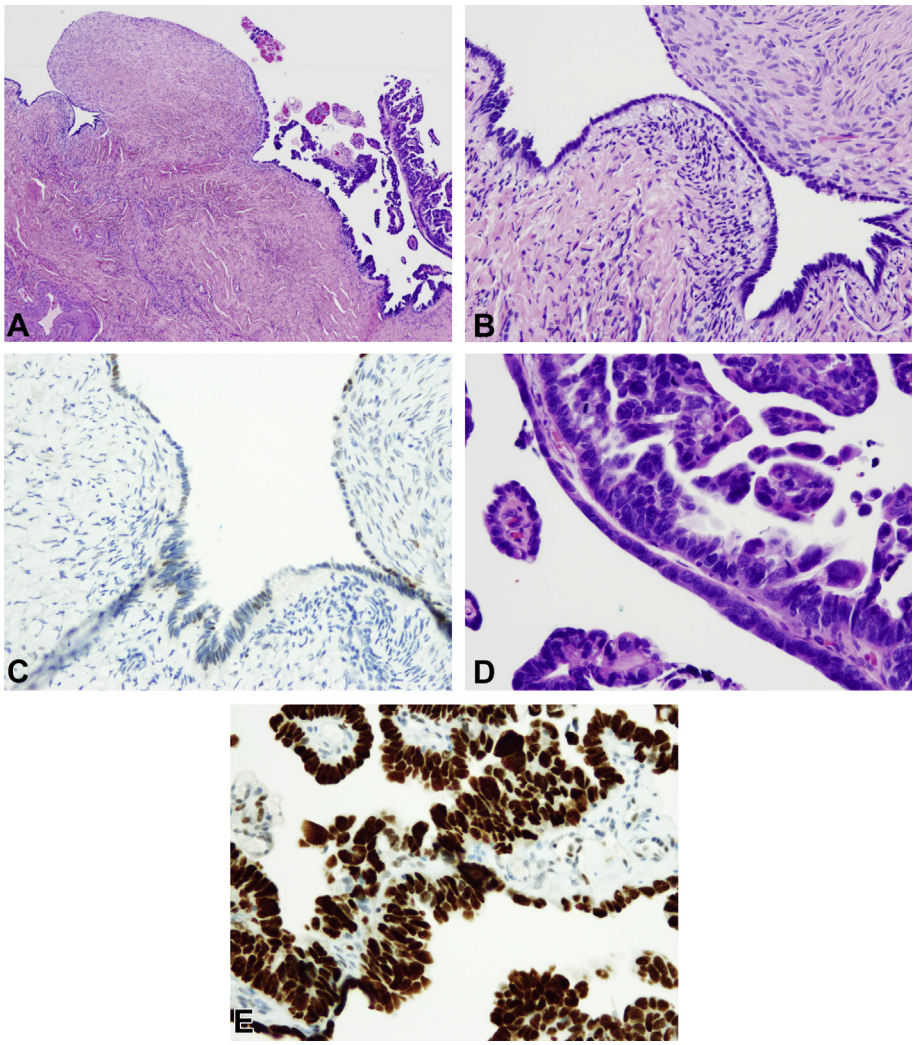

Fig. 1 Benign serous cystadenofibroma with focal high grade serous intraepithelial carcinoma. (A) Low power displaying cystadenofibroma architecture with benign epithelium (left) and high grade serous intraepithelial carcinoma (right). (B) High power of benign ciliated serous epithelium. (C) Same field as B showing 'wild-type' p53 immunostaining. (D) High power of pleiomorphic, multilayered, high grade serous intraepithelial carcinoma. (E) Same field as D showing dense uniform aberrant p53 immunostaining.

(borderline) epithelial patterns—either low grade ('atypically proliferative'[17]) or high grade ('non-invasive micropapillary carcinoma'[17])—and these foci were characterised by a multilayered, micropapillary, loosely cohesive epithelium with high grade nuclear features including hyperchromasia, pleiomorphism, prominent nucleoli and numerous mitotic figures. A MIB1 immunostain confirmed a high proliferation index in the high-grade areas but not in the adjacent benign epithelium. Likewise, a p53 immunostain showed normal (wild-type) nuclear staining of the benign epithelium (Fig. 1C) and strong, diffuse nuclear staining of the high-grade foci (aberrant pattern) (Fig. 1E). No strips of aberrant p53-staining secretory cell nuclei, analogous to so-called p53 signatures in fallopian tubes, were identified. These findings are consistent with focal intraepithelial HGSC arising directly from a benign serous cystadenofibroma. Extensive examination of the concurrently removed fallopian tubes failed to identify any putative serous epithelial precursor lesions, STIC lesions, p53 signatures, or secretory cell outgrowths.

The dualistic model grades serous malignancies as LGSC or HGSC based on nuclear grade and number of mitoses.[18] LGSCs are composed of cells with small, uniform nuclei and a low mitotic count, whilst HGSCs comprise cells with highly atypical, large, pleiomorphic nuclei with frequent (and often abnormal) mitotic figures. Necrosis and multinucleate tumour cells are also often present.[19,20] Serous carcinomas with intermediate nuclear features can be considered HGSC based on their clinical behaviour and molecular profile.[19] It is now generally accepted that LGSC and HGSC are biologically independent tumour types rather than being two ends of a single spectrum. LGSCs are uncommon, slow-growing, indolent tumours typically diagnosed in younger women, and usually confined to the ovaries (Stage I) at diagnosis. They are thought to arise in a step-wise manner, similar to the prototypical adenoma-carcinoma sequence in colorectal cancers, progressing from benign cystadenomas/cystadenofibromas through low grade (atypically proliferative) or high grade (micropapillary) borderline tumours to LGSC.[20,21] At a molecular level the majority of these tumours have activating mutations in the oncogenes *KRAS*, *BRAF* and *ERBB2*, which are members of the mitogen-activated protein kinase (MAPK) pathway. These mutations lead to constitutive activation of the MAPK pathway and uncontrolled cell proliferation.[22] *NRAS* is another MAPK pathway gene that has

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