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GYNAECOLOGICAL PATHOLOGY

Synchronous tumours of the female reproductive tract

C. Blake Gilks[1,2] and Friedrich Kommoss[3]

[1]*University of British Columbia, Department of Pathology and Laboratory Medicine, Vancouver, Canada;* [2]*Vancouver General Hospital, Division of Anatomical Pathology, Vancouver, Canada; and* [3]*Institute of Pathology, Friedrichshafen, Germany*

Summary

Many ovarian endometrioid carcinomas present with concurrent endometrial carcinoma, and these organ-confined, low-grade synchronous endometrial and ovarian tumours consistently behave as independent primary tumours, rather than a single advanced-stage carcinoma; they are associated with a very favourable prognosis and there is no need for adjuvant treatment. This phenomenon of synchronous tumours involving two or more sites within the female reproductive tract is well recognised, occurring in 1–2% of cases. Although some tumours can be recognised as metastasis, in many the relationship between the synchronous tumours is uncertain. Recently, application of next generation sequencing to synchronous endometrial and ovarian carcinomas has shed light on the relationship between these tumours, but raised more questions about the biology of this curious phenomenon. Herein, we review synchronous tumours involving more than one site in the female genital tract, discuss the pathogenesis, and offer guidelines for how to handle in routine practice.

Key words: Synchronous; independent primaries; metastasis; pseudometastasis.

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INTRODUCTION

In this review we will discuss those not infrequently encountered situations where tumours involve more than one site in the female reproductive tract at presentation. Synchronous independent tumours have been estimated to occur in 1–2% of all women with gynaecological cancers.[1–4] This finding immediately raises the important question of whether one tumour is primary and the other metastatic (and if so, which is the primary), or whether these are independent primary tumours that have arisen because of either a common environmental stimulus such as high body mass index with increased endogenous oestrogen, or underlying genetic predisposition, e.g., Lynch syndrome. Each combination of sites where synchronous tumours can occur will be discussed separately, as they have unique aspects; we will then offer general comments on the phenomenon of synchronous tumours of the female reproductive tract, including how to handle them in routine surgical pathology practice.

SYNCHRONOUS TUMOURS OF FEMALE REPRODUCTIVE TRACT AND GASTROINTESTINAL OR URINARY TRACT

Although this review is focused on synchronous tumours occurring at two (or more) sites within the female genital tract, it is worth commenting briefly on the phenomenon of synchronous tumours involving the female genital tract and either the gastrointestinal or urinary tract. Examples of synchronous tumours involving the female reproductive organs and gastrointestinal sites include carcinomas of stomach, colon or vermiform appendix, including low-grade appendiceal mucinous neoplasms with ovarian involvement[5–8] (Fig. 1). Although we include these as synchronous tumours (gastrointestinal and ovarian tumours usually present at the same time but the ovarian tumour may be the initial manifestation), the ovarian tumours have been proven to be metastases from the gastrointestinal tract, and it is safe to conclude that the concept of there being an increased likelihood of synchronous independent primary tumours of the gastrointestinal tract and ovary is no longer tenable, other than in patients with hereditary cancer predisposition syndromes such as Lynch syndrome (colonic adenocarcinoma and endometrioid or clear cell ovarian carcinoma) or hereditary breast and ovarian cancer syndrome with germline BRCA2 mutations (high-grade serous carcinoma of tube/ovary and pancreatic adenocarcinoma), discussed below. Moving away from this notion was a gradual process, as molecular data were accrued. For example, it was long thought that synchronous ovarian mucinous neoplasms and appendiceal low-grade mucinous tumours were independent primary tumours, or even primary ovarian tumours, based on both morphological features[9,10] and early molecular studies that, in retrospect, lacked sufficient discriminating power to prove or disprove a clonal relationship between the ovarian and appendiceal tumours.[11] With site-specific immunomarkers and more in-depth mutational analysis, it was accepted that these were appendiceal primary tumours with ovarian metastases[12,13] (Fig. 1B,C). It is important to note that such a shift in understanding is usually gradual, without a clear tipping point, and in some of the examples we will discuss in this review this shift is still in progress; there are, for example, pathologists who are skeptical of the clonal relationship between synchronous endometrial and ovarian carcinomas, or of the tubal origin of extra-uterine high-grade serous carcinoma, with ovarian involvement being metastatic.

Another example of synchronous tumours of gastrointestinal or urinary tract and female reproductive tract is Paget's disease. The 'association' of vulvar Paget's disease with 'underlying malignancies' has long been recognised, but only since the introduction of lineage-specific immunomarkers has it been appreciated that Paget's disease in the vulva represents two diseases: (1) primary vulvar adenocarcinoma, possibly originating from the ano-genital mammary-like glands, and (2) secondary involvement of vulvar skin by a

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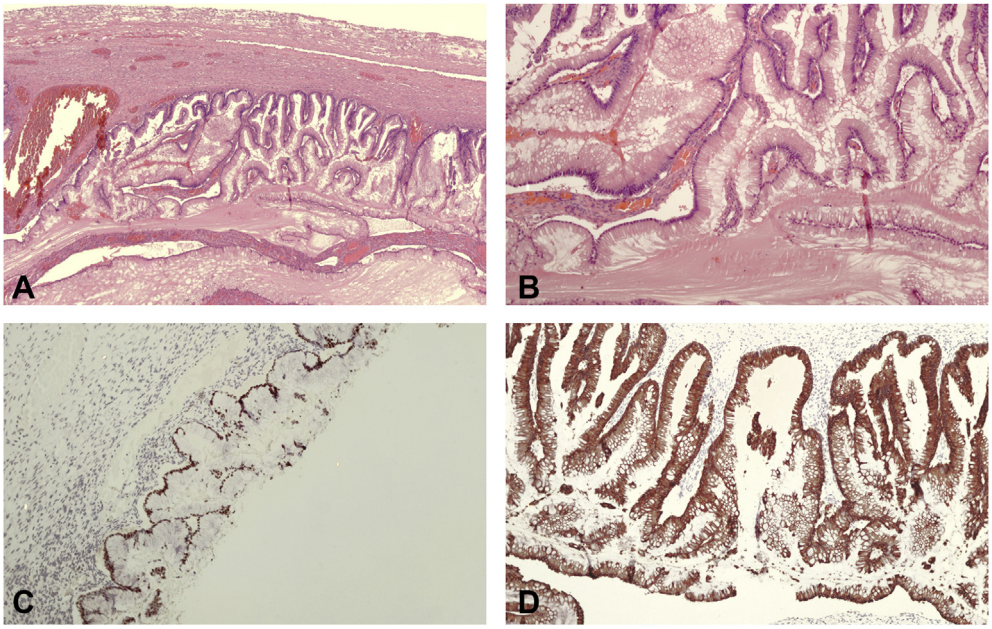

Fig. 1 Metastatic low-grade mucinous appendiceal mucinous neoplasm to the ovary: (A,B) H&E, (C) SATB2, and (D) CK20. Note the range of atypia from benign-appearing to 'borderline' in B.

primary anorectal, bladder or cervical carcinoma.[14–16] The former accounts for a large majority of Paget's disease of the vulva (approximately 95% in our experience).[15] Pagetoid involvement of vulvar skin secondary to a primary anorectal carcinoma (CK20+, SATB2+), or primary transitional cell carcinoma of the bladder (GATA3 and p63+) can be distinguished from primary vulvar Paget's disease (CK7+, CK20−) based on the immunophenotype.

A few observations can be made that are also relevant to synchronous tumours within the female reproductive tract. Firstly, metastases to the female genital tract organs are common, especially to the ovary. Secondly, ovarian metastases can be much larger than the primary tumour and be the initial presentation. The 'dominant mass' approach, in which the primary site of origin is deemed to be that with the largest mass, can be misleading, as ovarian metastasis can attain very large size, potentially attributable to the lack of constraints on growth. As a rule of thumb, when dealing with synchronous ovarian and extragenital tumours, the extra-ovarian tumour is typically the primary, especially if there is bilateral ovarian involvement, surface involvement, multinodularity, or hilar lymphatic invasion. However, it is worth noting that the most common source of metastatic tumours within the female genital tract is from other genital tract organs (whether by direct extension, intraluminal spread, i.e., endometrium to cervix or vagina, or transcoelomic spread, e.g., from endometrium or fallopian tube to ovary). The FIGO staging system recognises this propensity to metastasise first within the genital tract, and for these metastases to be associated with a more favourable prognosis (and lower stage) than metastases to sites outside the pelvis, and the remainder of this review therefore focuses on synchronous tumours of the female reproductive organs.

HEREDITARY CANCER SUSCEPTIBILITY SYNDROMES

Hereditary cancer syndromes, in which patients are at markedly increased risk of development of cancer because of a germline mutation in an antioncogene, were only recently recognised, and even more recently understood at the molecular level. There are two relatively common autosomal dominant hereditary cancer syndromes: Lynch syndrome[17–23] and hereditary breast and ovarian cancer syndrome.[24–26] The former, although named after Henry Lynch for his pioneering work in hereditary cancer susceptibility syndromes, was first described in detail by Alfred Scott Warthin, of the University of Michigan. However, the hereditary breast and ovarian cancer syndrome was first described by Lynch. Both syndromes are a result of germline mutations in genes involved in DNA repair; DNA mismatch repair enzymes in Lynch syndrome, and BRCA1 and BRCA2, both associated with homologous repair of double strand DNA breaks, in hereditary breast and ovarian cancer syndrome. Mutations in other genes can be associated with Lynch syndrome or hereditary breast and ovarian cancer syndrome, but are uncommon.[27] Both syndromes affect approximately 1 in 400 individuals in North America, and are associated with an increased risk of development of cancers of the female genital tract. Approximately 4% of endometrial carcinomas are associated with Lynch syndrome, while 15–20% of high-grade serous carcinomas of ovary/fallopian tube (but not other histotypes) are associated with hereditary breast and ovarian cancer syndrome. There is a 10% lifetime risk of developing ovarian carcinoma in patients with Lynch Syndrome, but the tumour histotypes are those associated with endometriosis, typically endometrioid and clear cell carcinoma.[23]

Although one might expect synchronous tumours of endometrium and colon to occur in patients with Lynch syndrome, as there is increased risk for both, this is a rare association in practice, and patients who develop more than one primary tumour will have a metachronous presentation of those tumours in most instances. Pathological features including location of tumour, morphology, and a limited panel of immunostains (e.g., ER, CK7, CK20, SATB2) can easily establish the independent nature of the endometrial and colonic tumours.

Aside from the hereditary cancer susceptibility syndromes, rarely unrelated synchronous independent tumours are co-

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