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Gynaecological neoplasms in common familial syndromes (Lynch and HBOC)

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Summary

Recognising hereditary predisposition in a cancer patient has implications both for the patient and the patient's kindred. For the latter, cascade germline testing can reassure those not-at-risk family members while carriers can be enrolled in cancer screening and prevention programs that are medically effective and economically sustainable for health care systems. Furthermore, in many of these syndromes, ramifications of molecular phenotypes are increasing, and it is now emerging that, in addition, they convey prognostic and predictive information. Although cancer predisposition syndromes are rare, these molecular phenotypes also occur as somatic events in sporadic cancer settings. The information obtained from these molecular phenotypes, regardless of germline or somatic origin, is being incorporated into clinical management in view of their manifold significance. Thus, increasingly, bespoke management of cancer patients involves testing for both germline and somatic mutations in tumours.

Lynch syndrome and *BRCA-1* and *BRCA-2*-associated hereditary breast and ovarian cancer are hereditary cancer syndromes frequently involving the gynaecological tract but tumours associated with similar molecular alterations may also occur sporadically. Thus, the molecular phenotype of mismatch repair deficiency, microsatellite instability or hypermutator phenotype may be attributable to germline or somatic events. Similarly, homologous recombination deficiency or '*BRCA*ness' in ovarian cancers may be syndromic or sporadic. While hereditary syndromes are well recognised, the prognostic and predictive implications of these molecular phenotypes have only recently been elucidated and these aspects will finally ensure that molecular screening may become standard of care. Thus, nowadays pathologists are asked to designate the molecular phenotype of these cancers and then determine whether it is due to hereditary or sporadic causes.

Key words: Lynch; MMR; endometrial cancer; BRCA; ovarian cancer; screening.

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LYNCH SYNDROME

Introduction

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome attributable to germline mutations in mismatch repair (MMR) genes, most commonly *MLH1*, *PMS2*, *MSH2*, *MSH6* and *EPCAM*. LS patients are at significantly elevated lifetime risk for several cancers including colorectal (CRC), endometrial (EC) and ovarian cancer (OC) as well as cancers of the stomach, urinary tract, hepatobiliary tract, small intestine, sebaceous glands and brain. The cumulative lifetime risk of EC for LS women is ~60% (27–71% depending on the MMR gene mutated, with highest risk being in the setting of *MSH6* mutation), exceeding that of CRC,[1–3] while the reported lifetime risk for OC is ~4–14%.[4–6] More importantly, ~60% of these women will present with a gynecological malignancy as the sentinel cancer.[7,8] Recognition of LS in women at this juncture allows implementation of highly effective CRC screening and prevention programs. Even though LS only accounts for ~2–6% of EC and ~2% of OC,[9–12] overall 20–30% of ECs[9,11,13] and 10% of OCs[14–16] are mismatch repair deficient (MMRd) with *MLH1* methylation accounting for most sporadic cases. Recently biallelic somatic inactivation of MMR genes has been implicated in a significantly smaller proportion of sporadic tumours.[11,16–20]

Pathological features of endometrial and ovarian cancer

Data suggest that all subtypes of EC may be encountered in LS, with a distribution similar to that observed in the sporadic population.[7,21–23] Although some studies have found a relatively higher number of the non-endometrioid or ambiguous endometrial cancers,[24–26] endometrioid carcinoma is the predominant histotype in LS-associated and sporadic MMRd. As EC cell type classification has moderate reproducibility even among experts,[27] it is recommended that pathologists avoid any histotype specific LS screening strategy in EC. There are fewer studies of LS/MMRd associated OC and they are limited by small sample sizes and variable inclusion criteria regarding MMRd definition.[28] Furthermore, prior to recent refinements of the morphological criteria of OC subtypes, pathological diagnosis was only moderately reproducible. Applying contemporary criteria, it has been

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shown that there is an almost exclusive association between MMRd/LS and endometrioid, clear cell, undifferentiated morphology or admixtures of the aforementioned subtypes in well-established LS-OC series and in MMR-IHC deficiency tissue microarray studies.[28–33]

Based on CRC studies, several seminal morphological observations have been made regarding MMRd associated EC (Fig. 1); namely, brisk immune response manifested as peri-tumoural and tumour-infiltrating lymphocytes (TILs),[22,23,34,35] mucinous differentiation,[36] morphological heterogeneity (mixed endometrioid clear cell and dedifferentiated endometrioid subtypes (Fig. 2)[23,34,37–41] and a predilection for localisation to the lower uterine segment.[7,26,39] While these observations have provided biological insights, especially regarding potential response to immunotherapy, the data indicate that their predictive value is insufficient to reliably triage EC for MMRd/LS screening.[9,42] MMRd has also been associated with higher grade, lymphovascular invasion and higher stage in EC by most studies.[35,39,40,43,44]

Prophylactic specimens from LS carriers

With the introduction of universal MMRd testing, more LS carriers will be identified, and with that an increase in the number of prophylactic specimens from LS carriers can be expected. Typically incidental EC is seen in ~10% of prophylactic hysterectomies[7,45–49] but precursor lesions [complex atypical hyperplasia (CAH)/endometrial intraepithelial neoplasia (EIN)] may be seen in up to 24% of hysterectomy specimens.[7,47,48] The incidental uterine cancers may be visible at time of grossing or may be occult. The vast majority of these cancers are low-grade/low-stage endometrioid carcinomas, but high-grade endometrioid and non-endometrioid carcinomas have been rarely reported and there is a single report of an incidental high-grade uterine EC with a synchronous incidental mixed clear cell and endometrioid carcinoma of the fallopian tube.[50,51] Based on the relatively high frequency of these incidental findings, we recommend preoperative biopsy/curettage or intraoperative assessment to ensure that appropriate surgery is performed should carcinoma be present. In terms of grossing, unless a gross lesion is present, we recommend submitting endometrium *in toto*, as most incidental lesions are microscopic.[7,48] Based on the OC subtypes implicated in LS, standard representative sections of tube and ovary are adequate.

Laboratory testing for mismatch repair deficiency

Laboratory testing for LS is typically sequential, with tumours first being screened for MMRd using either mismatch repair immunohistochemistry (MMR-IHC) or microsatellite instability (MSI) with subsequent germline and possible somatic testing following patients informed consent. The Bethesda panel was optimised for CRC and is applied generically to other cancers. Although studies on EC are relatively limited compared to CRC, several groups have now shown that MSI testing using the commonly used Bethesda pentaplex panel (2 mononucleotides and 3-dinucleotide

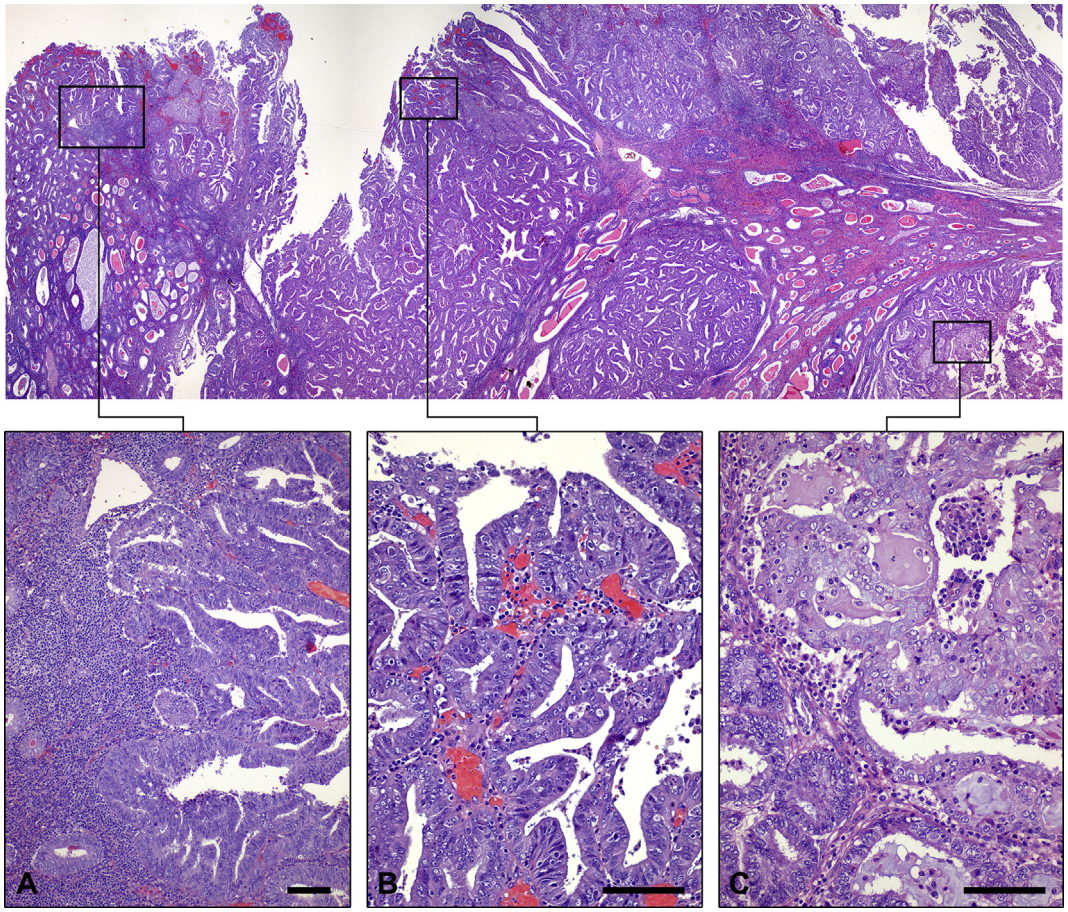

Fig. 1 Endometrioid endometrial carcinoma from a LS patient. (A) Note the peritumoural lymphocytes, (B) the tumour-infiltrating lymphocytes and (C) mucinous differentiation. Scale bar = 100 μm.

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