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Review

Current status of diagnosis for synchronous endometrial and ovarian carcinomas by molecular biological approach

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The diagnosis of synchronous carcinomas is difficult in all types of cancer. However, in gynecological cancers, synchronous endometrial and ovarian carcinomas are rarely seen and are more difficult to diagnose because the uterus and ovaries are adjacent organs. Although classical pathological criteria have been used for diagnosis, molecular biological methods are increasingly being used to refine diagnostic decisions. Through genomic analyses, such as next-generation sequencing and targeted and exome sequencing, many cases that have been diagnosed and treated as primary synchronous carcinomas have been determined to actually be metastatic carcinomas. It is necessary to establish new diagnostic criteria by incorporating molecular biological methods with conventional pathological diagnosis.

Keywords

Synchronous endometrial and ovarian carcinoma; Molecular biological approach; Genomic analyses; Next-generation sequencing; Targeted and exome sequencing

1. Introduction

Synchronous carcinomas make up 0.5%–1.7% of gynecological cancer cases [1]. Of these, the incidence of synchronous endometrial and ovarian carcinomas (SEOC) is the highest, occurring in 5% of patients with endometrial carcinomas and 10% of patients with ovarian carcinomas [2]. Determining whether synchronous carcinomas are separate simultaneous primary carcinomas or metastases is important for treatment and prognosis. Synchronous carcinomas are often detected at an early stage and are characterized by a slower progression and a better prognosis than single carcinomas [3–6]. Compared with endometrial carcinomas, synchronous carcinomas show no difference in the 5-year survival rate, but the prognoses for the 10-year survival and overall survival rates are better [4, 6, 7]. In comparison with ovarian carcinoma, the 5-year progression-free and overall survival rates are higher in synchronous carcinomas [4–6, 8]. Prognostic factors include age, menopause status, stage of ovarian carcinoma, lymphadenectomy, grade of endometrial carcinoma, metastasis of omentum, and residual tumor [7]. On the other hand, in synchronous carcinomas wherein both endometrial and ovarian cancers are stage IA, synchronous status had no significant effect on prognosis [9]. Therefore, determining whether a carcinoma is synchronous or metastatic is necessary for a more accurate prognosis.

2. Current status of diagnosis by molecular biological approach

2.1 Classical pathological diagnosis

Differentiation between synchronous and metastatic carcinomas based on clinical symptoms is difficult and requires pathological evaluation. The pathological criteria for synchronous carcinomas are listed by Ulbright and Roth [10] as follows: different histologic types as major criteria, both tumors confined to primary sites; no direct extension between tumors; no lymphovascular tumor emboli; no or only superficial myometrial invasion; and no distant metastasis as minor criteria. If the major criteria or all minor criteria are filled, the tumors are diagnosed as synchronous primary carcinomas. Subsequently, Scully *et al.* [11] greatly improved the classification of patients with endometrial and ovarian carcinomas into three groups and described the clinicopathological details of each: primary endometrial carcinoma with ovarian metastases, primary ovarian carcinoma with endometrial metastases, and synchronous primary endometrial and ovarian carcinomas. Diagnoses of synchronous and metastatic carcinomas has been based on histological similarities and invasion patterns, such as the criteria set out by Ulbright and Roth and Scully *et al.* [11] Recent the World Health Organization (WHO) classification of tumours for female genital tumours suggests the following features as suggestive of metastases; bilateral ovarian involvement, small ovarian tumour size, capsular/surface involvement, predominantly hilar distribution, vascular invasion, absence of a precursor lesion, and high tumour grade [12]. Deep myometrial invasion and the presence of lymphovascular invasion in the uterine corpus also suggested metastasis [12]. The two most common histological types of endometrial carcinoma involving the ovaries are endometrioid and serous. Since serous carcinoma is more likely to metastasize, ovarian metastases qualify as stage IV disease and have a poor outcome, the essential and desirable diagnostic criteria listed below should be used to make a careful diagnosis; essential: clinical features and macroscopic appearance favouring a metastasis,

desirable: ovarian surface and superficial cortex involvement, hilar and lymphovascular space involvement, histological features suggestive of a primary tumour other than an ovarian primary, an infiltrative growth pattern with stromal desmoplasia/nodular growth pattern and immunohistochemical profile [12].

2.2 Diagnosis by molecular biological methods

In recent years, molecular biological methods are being implemented for diagnosis. In a study by Chao *et al.* [13], 13 out of 14 (92.8%) of synchronous endometrial and ovarian endometrioid carcinomas harbored 2 to 34 (median, 3.5 mutations) identical somatic single nucleotide variants and short insertion/deletions. These 13 pairs of synchronous carcinomas had high clonality indices very close to one and were deemed clonally related. The clonal relationship determined by genomic analyses did not agree with clinicopathological criteria in 11 of 14 cases. Anglesio *et al.* [14] found 17 of 18 patient cases of SEOC from the series showed evidence of a clonal relationship based on both targeted and exome sequencing. Furthermore, Schultheis *et al.*'s [15] findings from whole-exome massively parallel sequencing suggested that sporadic synchronous early stage endometrioid endometrial carcinomas and endometrioid ovarian carcinomas are clonally related and likely involved dissemination from one site to the other. In these studies, clonality was found to be similar in the majority of cases histopathologically diagnosed as synchronous carcinomas of different primary. This suggests that the majority of cases histopathologically diagnosed as independent synchronous carcinomas may in fact be dissemination from one carcinoma to the other. However, it is also necessary to consider the possibility that the genetic variants in endometrial and ovarian carcinomas are the same, even if they are independent. Research is underway to determine which gene variants should be examined in the diagnosis of synchronous carcinomas. Next-generation sequencing of a panel of 73 genes in 22 cases of synchronous endometrial and ovarian endometrioid carcinomas confirmed a clonal origin in all cases by at least one shared variant in *PTEN*, *AKT1*, *PIK3CA*, *KRAS*, *TP53*, and *ARID1A* [16]. In another study, the frequencies of somatic variants in *TP53*, *PTEN*, *CTNNB1*, *KRAS*, and *POLE* were 3 (37.5%), 2 (25.0%), 3 (37.5%), 0 (0.0%), and 5 (62.5%) of 8 cases of ovarian tumors and 3 (37.5%), 2 (25.0%), 3 (37.5%), 1 (12.5%), and 5 (62.5%) of 8 cases in endometrial tumors, respectively [17]. Furthermore, Reijnen *et al.* [18] demonstrated SEOC were enriched for *PTEN* and *CTNNB1* variants and harbored less *TP53* variants than metastatic cases. These studies suggest that it is not necessary to examine a large number of variants to diagnose for synchronous carcinomas. However, the presence of variants in genes such as *PTEN*, *AKT1*, *PIK3CA*, *KRAS*, *TP53*, *ARID1A*, *CTNNB1*, and *POLE* may contribute to the diagnosis. In addition, such molecular diagnosis may be useful in multiple carcinomas. In a case report of a triple carcinoma patient who developed endometrial and ovarian carcinomas, as well as lung carcinoma, *CTNNB1* and *PIK3CA* variants were detected in the three organs, whereas *PTEN* and *ARID1A* variants were detected in the endometrial and ovarian carcinomas, but not in the lung [19]. In multiple carcinomas, it is even more difficult to determine whether the carcinoma is primary or metastatic compared with double carcinomas. Thus, the molecular biological approach should be strongly considered in such cases. In addition, synchronous endometrial and ovarian carcinomas can be seen in the hereditary disease Lynch syndrome. Lynch syndrome is implicated in 2%–6% of endometrial carcinomas and 0.4%–1% of ovarian carcinomas. Ten to 15% of patients with Lynch syndrome develop endometrial cancer, and 28%–60% develop ovarian cancer during their lifetime [20, 21]. Interestingly, origins for SEOC in Lynch syndrome (LS) shared the similar degrees of concordance between complex hyperplasias as same as sporadic cases [22]. Lynch syndrome is caused by variants in the mismatch repair (MMR) gene and has microsatellite instability (MSI) [23]. It is sometimes suggested that all patients with SEOC should undergo MSI or immunohistological analysis of MMR [24]. SEOC in Lynch syndrome patients may represent distinct primary tumors although a subset of MMR-deficiency syndrome-related SEOC may originate from a single primary tumor at variance with their clinical diagnosis, with the endometrium being the likeliest site of origin [25]. However, it has been reported that most synchronous carcinomas are not hereditary, but sporadic [26]. Further studies are needed on the usefulness of assessing MSI and MMR protein expression in patients with synchronous carcinomas. The *BRCA* gene, which has been reported to be pathologically mutated in 14.7% of all ovarian cancers [27], does not appear to be a risk factor in SEOC [28].

3. Conclusions

The diagnosis of SEOC is one of the most difficult issues in clinical practice and has traditionally been based on classical pathology. Recent results from molecular biological approaches; however, suggest that many of the cases that have been diagnosed and treated as duplications may not be primary synchronous carcinomas but metastatic carcinomas. We must establish new diagnostic criteria that incorporate molecular biological methods with conventional pathological diagnosis and take SEOC diagnosis to the next stage.

Author contributions

YK and KN have given substantial contributions to the conception or design of the manuscript. KB, DA to the supervision. YK to the writing original draft. KN, KB and DA to the review and editing. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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