Letters to the Editor


The simultaneous development of carcinomas in the endometrium and the ovaries is a well-known phenomenon. In most cases, they are two independent primary tumors, but in some others, there is a primary tumor in one location with metastatic spread to the other location. Several clinicopathological features can be used in this differential diagnosis: (a) stage; (b) size; (c) histological type and grade of the tumors; (d) the presence and extent of blood vessel, tubal, and myometrial invasion; (e) bilaterality and pattern of ovarian involvement; (f) coexistence with endometrial hyperplasia or ovarian endometriosis; and (g) follow-up of the patients (1). By paying attention to these features, the precise diagnosis is easy to make in most of the patients. However, individual cases may pose problems in differential diagnosis. Several years ago, we demonstrated that comparison of immunohistochemical and DNA flow cytometric features of both tumors in each case could be of some help, but we concluded that differential diagnosis relied largely on conventional clinicopathological findings (2).

Several investigators have studied the possible value of some molecular pathology techniques for the distinction between metastatic and independent tumors in this setting. They included LOH (3, 4), clonal X inactivation (5), and MI (4) analyses. Although these techniques have proved to be useful in individual cases, their results should be interpreted with caution and always in concordance with the clinicopathological features.

For example, it has been shown that different LOH patterns in two tumor components do not necessarily indicate a different clonal origin because different patterns of LOH can be demonstrated at distant parts of the same tumor as a result of tumor heterogeneity (6). Similarly, demonstration of identical X chromosome inactivation patterns in two components of the same tumor should not be taken as an indication that both have a common clonal nature; indeed, there is a 50% probability that they could be of different cell origin (5).

Mutation analysis of genes involved in the early steps of tumorigenesis is the best way to assess the common origin of two different tumor components. In their article in Clinical Cancer Research, Lin et al. (7) studied the presence of PTEN mutations in independent and metastatic carcinomas involving the endometrium and the ovaries. Theoretically, PTEN is an excellent candidate to be used in this differential diagnosis; PTEN mutations are involved in early steps of endometrial tumorigenesis (8, 9), and they also occur in endometrioid carcinomas of the ovary (10).

In an ongoing investigation on the impact of several molecular alterations in endometrial carcinomas (11–14) as well as in the differential diagnosis between independent and metastatic endometrioid carcinomas of the endometrium and the ovary, we have studied a case in which two obvious independent primary tumors presented the same PTEN mutation in both neoplasms. The case fulfilled the conventional clinicopathological criteria for independent primary tumors: (a) pathologic examination of the uterus revealed a small grade II (FIGO) endometrioid carcinoma of the endometrium that infiltrated less than one-third of the myometrial wall without blood vessel, tubal, or cervical invasion; and (b) the right ovary had a grade I (FIGO) endometrioid carcinoma (9.5 cm, greatest diameter) that was found to arise from an old endometriotic cyst. Moreover, follow-up seemed to confirm the independent nature of the neoplasms; the patient is well and has been without evidence of disease for 4 years after surgery. Molecular pathology findings gave further support to the independent clonal origin of both tumors. The endometrial carcinoma exhibited MI (which was not present in the ovarian tumor) in three CA repeat microsatellite repeats and mononucleotide tracts BAT-25 and BAT-26, and both tumor components showed different X chromosome inactivation patterns by the HUMARA assay. However, the same PTEN mutation (404–405insT) was detected in the two neoplasms.

The only possible explanation for this result is that a common carcinogenic agent could be theoretically capable of inducing the same genetic abnormality in two different tumors that developed as a result of a field effect in two closely related tissues, namely, the endometrium and the ovaries. We believe that this single case is not anecdotal, and it can clearly illustrate a frequent phenomenon. Interestingly, Lin et al. (7) were surprised by the fact that two cases initially interpreted as independent tumors were reclassified as metastatic because of the finding of identical PTEN mutations in both tumor components. By following the conventional clinicopathological analysis, these two cases could be interpreted as true independent neoplasms.

In our opinion, molecular pathology analyses may be helpful in the discrimination between independent and metastatic endometrioid carcinomas of the endometrium and the ovaries; however, we think that they should always be interpreted in light of the conventional clinicopathological findings. It also appears that the best way to approach this differential diagnosis from a molecular viewpoint is to combine the different available techniques (LOH, clonal X chromosome inactivation, and MI, and gene mutation analyses). Each of these techniques has limitations, but their combination may provide important information, particularly in cases showing inconclusive clinicopathological features.

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1 The abbreviations used are: LOH, loss of heterozygosity; MI, microsatellite instability.
Reply

We thank Dr. Matias-Guiu and colleagues for their interest in our article (1). We agree that there are objective histopathological criteria used to identify synchronous endometrial and ovarian carcinomas, because this clinical entity exists in nearly 25% of all diagnosed endometrioid ovarian carcinomas. Clinical decisions have been successfully made based on these criteria. However, molecular analyses of tumors are rapidly identifying subsets of neoplasias that confer improved or dismal patient outcomes by indolent or aggressive tumor biology such as in BRCA1+ (2) or p53-null ovarian cancers (3), respectively, although these lesions share common histopathological features. In addition, the clonal origin of neoplasia as well as normal epithelium is currently being defined (4–6).

Previous authors have agreed that identical gene mutations in two distinct tumor sites support the clonal origin of the tumor and subsequent metastasis (1, 5, 6) and, in fact, have even suggested clonal migration (6). We have shown that identical PTEN mutations identified in the primary endometrial cancer were also seen in all of the metastatic lesions tested. Patterns of loss of heterozygosity showed heterogeneity and were not reliable for clonality studies. We did not use X inactivation in this study, but it would be important to test the known metastatic cases to determine the accuracy of the human androgen receptor gene test. Molecular techniques such as direct mutation analysis, loss of heterozygosity, microsatellite alteration, and X chromosome inactivation have been used alone and in combination by many authors addressing the issue of clonality. Tumor heterogeneity makes analyses difficult, particularly when the exact “early event” is unknown. PTEN alteration has been shown to be an early event in endometrial carcinomas (7).

The case described by Matias-Guiu and colleagues fulfilled the pathological criteria for synchronous tumors. The endometrial and ovarian tumor had identical mutations (404→405insT) but different X chromosome inactivation patterns and MI1 was described in the endometrial tumor. First, germ-line mutation must be eliminated as a possible reason for this observation. The interesting point in this case is that the ovarian tumor arose on the background of endometriosis and may actually represent malignant degeneration of a migratory endometrial cell. The clonal status of endometrioid ovarian cancer to the endometriotic implant has been described previously (8). Therefore, one must consider a common source of the tumors in this case. The microsatellite pattern is also of interest because PTEN mutations occur in over 75% of MI-positive endometrial cancers (7), and it would be helpful to know whether the standard panel of MI markers were used and whether any MI was identified in the ovarian tumor. Also, the 404→405insT mutation seen in these tumors occurs in a small holopolymeric tract of four Ts and may represent a replication error to the precursor cells. It is more difficult to explain the different pattern of X chromosome inactivation. The authors did not describe the result, and one must consider the possibility of stromal or lymphocyte contamination as a source of this discrepancy. Another consideration is the possibility that a somatic mutation (a slip in DNA replication and the addition of a single T nucleotide) occurred early in embryogenesis during the development of the upper genital tract, perhaps before a delayed X inactivation occurs. Analysis of nontumorigenic endometrium and/or the opposite ovarian epithelium may help to negate this possibility.

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1 The abbreviation used is: MI, microsatellite instability.
We feel that the single case presented does not warrant the conclusion that common PTEN mutations are not helpful in diagnosing synchronous versus metastatic tumors of the endometrium and ovary. Rather, additional studies are needed to define the accuracy of the molecular testing in good controlled studies of known metastatic lesions compared with the suspected synchronous primary tumors.

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References

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