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Malignant melanoma metastatic to the ovaries: a clinicopathological and immunohistochemical study of four cases

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Introduction: Ovarian involvement with malignant melanoma (MM) is extremely rare often leading to a misdiagnosis of ovarian cancer. We present the clinicopathological and immunohistochemical features of four cases of ovarian metastatic MM diagnosed at our Department over a 23-year period (1989–2011).

Materials and Methods: The patients' age ranged from 28 to 72 (mean 49.5) years. All presented with a pelvic mass and a past history of MM (three cutaneous, one anorectal), although at the time of the histopathological evaluation it was known in only two cases. The interval between the primary and ovarian MM ranged from 3 to 72 months. The initial treatment was surgery, followed by chemoimmunotherapy in three of them. One patient died of an unrelated cause 29 months following surgery with metastatic disease, while the other three died from metastatic disease within 41 days, 15 months, and 10 years, respectively. Two of these patients had lymph node metastases previously and all three had synchronous metastases at other sites at the time of the surgery.

Results: The ovarian tumors were unilateral, varied in size from 14 to 25 cm, and only two were grossly pigmented. Histologically, they were composed of large epithelioid cells with eosinophilic cytoplasm, small cells, spindle-shaped cells, or a combination. The predominant architectural patterns were nodular in one, and diffuse in the other three tumors. Immunostains for S-100, HMB-45, and melan-A were positive in all tumors tested.

Conclusion: The presented cases illustrate the clinical variability and unpredictable biologic behavior of ovarian metastatic MM and emphasize the value of immunohistochemistry in establishing the diagnosis.

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***MED12* exon 2 mutations in common and histopathological variants of uterine leiomyoma and leiomyosarcoma**

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Introduction: Based on histopathology, uterine leiomyomas can be divided into various subtypes. Cellular, atypical and mitotically active leiomyomas are examples of variants of common leiomyomas. According to prevailing view, common leiomyoma is not the precursor of respective malignant tumor, uterine leiomyosarcoma, which is a relatively uncommon gynecological malignancy. However, the pathogenesis and histogenetic relationship of common leiomyoma, leiomyoma variants and uterine leiomyosarcoma has remained obscure. We recently showed that *MED12* (mediator complex subunit 12) exon 2 is mutated in approximately 70% of uterine leiomyomas (N Mäkinen *et al.* (2011) MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. *Science* 14, 252–255.). The mutation hot spot affects an evolutionary conserved region of the MED12 protein. MED12 is part of a 26-subunit protein complex, which is thought to regulate global as well as gene-specific transcription by bridging DNA regulatory elements to the RNA polymerase II initiation complex.

Materials and Methods: To address the molecular pathogenesis of uterine leiomyotumors, we studied the frequency of *MED12* exon 2 mutations in different histopathological forms of uterine leiomyoma (common, $n = 69$; cellular, $n = 67$; atypical, $n = 18$; mitotically active, $n = 26$) and leiomyosarcoma ($n = 25$) by direct sequencing.

Results: With the exception of mitotically active leiomyomas, histopathological variants and leiomyosarcoma harbored significantly less *MED12* exon 2 mutations than common leiomyomas.

Conclusion: This suggests that atypical and cellular variants represent biological entities distinct from common leiomyomas. The rarity of *MED12* exon 2 mutations in leiomyosarcomas (4%, 1/25 cases) indicates that *MED12* exon 2 mutation positive leiomyomas are unlikely precursors for leiomyosarcomas.

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Expression of CHOP and its correlation with human papillomavirus infection and p53 expression in squamous tumor of the uterine cervix

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Introduction: Recent studies have suggested that virus-induced endoplasmic reticulum (ER) stress modulated various signaling pathways for cell survival or cell death. CHOP is associated with the ER stress-mediated apoptosis and it is involved in carcinogenesis of several human cancers. P53 degradation by viral oncogene E6 of human papillomavirus (HPV) is central pathogenesis of uterine cervical cancer.

Materials and Methods: The expression of CHOP and p53 protein was analyzed using immunohistochemistry on tissue sections from 191 patients with invasive cancer or preinvasive lesions of uterine cervix (61 cases of squamous cell carcinoma (SqCC), 66 cases of cervical intraepithelial neoplasia (CIN) III, and 64 cases of CIN I). Information of high risk (HR)-HPV (HPV16, 18) status of the patients was obtained through a computerized database of the tumor registry.

Results: CHOP was expressed in 59.4% of CIN I, 48.5% of CIN III and 70.5% SqCC cases. CHOP expression was significantly higher in invasive carcinomas than in preinvasive lesions ($P = 0.042$). p53 expression gradually increased with tumor progression and was significantly higher in invasive carcinomas (91.8%) than in CIN I (57.8%) and CIN III (83.9%) ($P < 0.001$). HR-HPV infection was correlated significantly with CHOP and p53 expressions ($P = 0.009$, $P = 0.019$, respectively). CHOP expression was correlated with p53 expression ($P = 0.038$).

Conclusion: Our results suggest that CHOP is involved in the carcinogenesis of squamous cell carcinoma of the uterine cervix via association with HR-HPV and p53.