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The Relationship of Endometrialhyperplasia and Endometrial Polyps with P16 Stromal Expression: Review

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Öz

Endometriyal polipler çok yaygın benign endometriyal lezyonlardır, ancak patogenezleri ile ilgili çok çalışma yoktur. Endometriyal polipin histopatolojik tanısı basit olmasına rağmen, bir biyopsi veya küretaj örneğinde endometriyal polipi endometriyal hiperplaziden ayırmak genellikle zordur. Bu ayırıcı tanıda yardımcı olan bir immünohistokimyasal belirteç yoktur. Son zamanlarda endometriyal poliplerle ilişkili endometriyal seröz adenokarsinomların incelenmesinde p16 stromal ekspresyonu bildirilmiştir. Bu nedenle endometrial polipler bazı kaynaklarda preneoplastik oluşumlar olarak tanımlanmaktadır. Endometrial poliplerdeki bu farklı stromal hücre ekspresyonları nedeniyle, derleme yazımızda endometrial hiperplazi ve endometrial poliplerde stromal dokudaki p16 ekspresyonlarının ayırıcı tanıdaki yerini sunmak istedik.

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Abstract

Endometrial polyps are very common benign endometrial lesions, but there are not many studies on their pathogenesis. Although the histopathological diagnosis of an endometrial polyp is simple, it is often difficult to distinguish an endometrial polyp from endometrial hyperplasia on a biopsy or curettage specimen. There is no immunohistochemical marker that helps in this differential diagnosis. Stromal expression of p16 has recently been reported in the study of endometrial serous adenocarcinomas associated with endometrial polyps. For this reason, endometrial polyps are defined as preneoplastic formations in some sources. In our review of these different stromal cell expressions in endometrial polyps, we wanted to present the place of p16 expressions in the stromal tissue in endometrial hyperplasia and endometrial polyps in the differential diagnosis.

INTRODUCTION

Endometrial polyps are common lesions in gynecology that can cause abnormal genital bleeding(Silverberg, 1992). Histological diagnosis of endometrial polyps in hysterectomy materials is not difficult. The size and shape of the glandular structures in endometrial polyps, which are mostly recognized macroscopically with their polypoid configuration, differ (Reslová et al., 1999). In addition to cystic dilatations, which are frequently observed in glandular structures, the presence of thick-walled vessels in the stroma of endometrial polyps is

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remarkable when compared to normal endometriums(Silverberg, 2000). However, diagnosis of endometrial polyp can be challenging from time to time, since tissue integrity is impaired in curettage or incisional/punch biopsy samples and/or the sample is not from an area representing the lesion. Winker et al. (Winkler et al., 1984) determined that endometrial polyps are generally reported as endometrial hyperplasia in curettage and biopsies. This diagnostic confusion between endometrial hyperplasia, especially simple hyperplasia and endometrial polyp, which can be experienced outside of excisional biopsy materials, may cause problems in terms of patient management.

One of the most important histological distinguishing features between endometrial hyperplasia and endometrial polyp is the differences in stromal appearance. Thick-walled blood vessels in endometrial polyps are relatively easy to recognize and their vascular partners are different from other lesions. Endometrial hyperplasias, on the other hand, mostly arise in our abdomen with small spiral artery-like blood vessels (Allison et al., 2008). It has also been reported that glands lined up parallel to the surface epithelium are a useful histological feature for the diagnosis of endometrial polyps (Kim et al.,2004). However, there is still no useful immunohistochemical marker that can be used in the differential diagnosis of endometrial hyperplasia and endometrial polyp, especially in small and/or fragmented biopsies.

Recently, p16 stromal expression has been reported in the examination of endometrial serous adenocarcinomas associated with endometrial polyps (Huang et al,2011). Therefore, endometrial polyps are defined as preneoplastic formations in some textbooks (McCluggage, 2011). Due to these different expressions of stromal cells in endometrial polyps, we wanted to present the place of p16 expressions in stromal tissue in endometrial hyperplasia and endometrial polyps in the differential diagnosis in our review article.

P16

P16 is one of the most studied suppressor genes in human neoplasms (Malpica et al.,2010). It is a tumor suppressor protein encoded by the CDKN2A gene (9p21.3) (O'Neill et al., 2006). It prevents the cell cycle from progressing to the S phase. It inhibits cyclin D-dependent protein kinases (CDK4 and CDK6) and keeps Rb in its hypophosphorylated state. This prevents it from dissociating from the E2F transcription factor (O'Neill et al., 2006). Protein expression is frequently increased in senescent cells, triggering cell death and

apoptosis. In many non-HPV-related tumors, protein function is suppressed by mutations of epigenetic or genetic abnormalities, including promoter CpG methylation. For example, carcinoma of the colon, carcinoma of the breast, carcinoma of the pancreas, carcinoma of the head and neck (O'Neill et al., 2006, McCluggage, 2011).

DISCUSSION AND CONCLUSION

P16 is one of the most frequently used immunohistochemical markers in gynecopathology cases (Malpica et al.,2010). By showing strong nuclear immunoreactivity in high-risk HPV-related lesions and cytoplasmic immunoreactivity in cervico-vaginal neoplasms, it greatly helps in the differential diagnosis of benign and malignant (Huang et al,2011). Recently, it has been used as a p16 positive sensitive and distinctive marker in cases of endometrial serous adenocarcinoma and endometrial intraepithelial carcinoma (Keating et al.,2001). There are very few studies on p16 immunoreactivity in epithelial cells (Klaes et al.,2002). More studies have been conducted on gynecological lesions, excluding leiomyosarcoma and undifferentiated endometrial lesions (Chiesa-Vottero et al., 2007). Compared to leiomyomas, p16 shows more common and stronger staining in leiomyosarcomas (Yemelyanova et al.,2009).

P16 is a cyclin-dependent kinase-4 inhibitor (Gannon et al., 2007). The INK4a/ARF locus is encoded by a gene located on chromosome 9p21. The role of p16 in tumorigenesis is variable and the significance of high expression expression in the tumor is different (D'Angelo et al.,2010). High expression of p16 in tumors occurs by at least two different mechanisms (Carlson et al., 2008). It begins with an abnormality in the first Rb pathway. Normally, p16 inactivates CDK4/6 (Gannon et al., 2007, D'Angelo et al.,2010), blocks and induces phosphorylation of Rb, resulting in cell cycle arrest. Loss of this p16 function allows for uncontrolled cellular proliferation (Marotti et al., 2011). Also, other malignant tumors are p16 overexpression, well-known example HPV-related neoplasms. HPV oncoprotein E7 inactivates Rb, which causes p16 to be released from negative feedback control and an increase in p16 protein level (Romagosa et al.,2011). In some malignant tumors unrelated to HPV, p16 is also highly expressed by the mechanism resulting from deregulation of Rb (Serrano,1997). The second state of p16 overexpression is related to another important function of p16, oncogene-induced senescence (OIS). p16 induces cellular senescence in response to oncogene expression and cell cycle arrest (Munger et al., 1987). This mechanism is also seen in

neurofibroma and schwannoma benign tumors. These tumors overexpress p16 and acidic βgalactosidase activity associated with senescence, BRAF mutations, and cell cycle arrest (Schwartz et al., 1998). While the malignant counterparts of these tumors stain negatively for p16, overexpression of p16 in benign tumors suggests that it controls proliferation and appears to protect tumor cells from malignant transformation (Michaloglou et al.,2005). Since an endometrial polyp is a benign lesion, stromal p16 expression is probably explained by this latter mechanism (Sabah et al.,2006).

Although the endometrial polyp is considered a benign stromal neoplasm, data supporting this hypothesis are limited. Fletcher et al. they mentioned the clonal 6p21 gene in polyps limited to the endometrial mesenchymal component (Fletcher et al., 1992). Cin et al. it has been reported that there is HMGIC amplification in endometrial polyps and HMGIC gene expression in the nuclei of stromal cells in endometrial polyps (Cin et al.,1998). It is known that the HMGIC gene is expressed in a benign manner, and it has been reported that it is rarely found in mesenchymal tumors and malignant tumors (Moghrabi et al.,2007).

Several immunohistochemical studies have been conducted focusing on endometrial stromal cells. Normally functioning endometrial stromal cells are positive for calretinin (Mai et al.,2008). CD34 is positive in stromal cells at the base of the normal endometrium and in dysfunctional uterine bleeding and endometrial polyp. (Moghrabi et al.,2007, Mai et al.,2008). These studies imply that stromal cell change in various endometrial tissues, whether neoplastic or not, are abnormalities. The current study focused only on endometrial polyps and endometrial hyperplasia. It is unclear whether expression of p16 in endometrial hyperplasia, endometrial polyps indicates neoplastic stromal proliferation or non-neoplastic stromal abnormalities. To clarify this issue, it should be clarified whether stromal proliferation is clonal or not (Horree et al., 2007). The mechanism of p16 expression and its significance are not fully understood in non-neoplastic gynecological lesions. Horre et al. reported that p16 expressed was consistent in endometrial tubal metaplasia (Horree et al., 2007). In the current study, tubal metaplasia, eosinophilic cell change, and surface syncytial change were also p16-positive in addition to p16 expression in almost all foci. Although the mechanism of endometrial metaplasia is still unknown, it is possible that glandular differentiation p16 expression in the endometrium is possible.

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