Distinguished Expert Series

Molecular markers of miscellaneous primary and metastatic tumors of the uterine cervix

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Summary

Miscellaneous primary tumors of the uterine cervix are rare. Markers which can be utilized to detect these tumors are very few and in most cases, have not been clinically validated. The information provided in this article will help in developing strategies to discover novel markers and initiate translational research in this ignored area. Based on the reported studies, cytokeratin markers are common in many tumors and few of these rare cancers demonstrate human papilloma-virus (HPV) and Epstein Bar virus (EBV) infection. Due to the very low prevalence of these tumors, epidemiological studies have not been conducted and the etiology of these tumors is largely unknown.

Key words: Uterine cervix; Rare tumors; Markers; Metastatic.

Introduction

Any malignancy is considered rare if the global incidence rate is less than 40,000 annual cases. Although cervical cancer is the second most common malignancy in women worldwide in terms of both incidence and mortality, some cancers of the uterine cervix fall under this rare tumor category. These rare tumors of the uterine cervix may have a deceivingly benign characteristic. Some of the malignant tumors of this category are misinterpreted as less aggressive lesions and are reviewed in this communication.

In the uterine cervix, the two major neoplasms of this group are the minimal deviation adenocarcinomas i.e., mucinous and endometrioid types. The latter subtype has been described only recently. Endometrioid adenocarcinomas, usually of the uterine corpus, but occasionally of other sites, may have microglandular patterns that can lead to misdiagnosis, sometimes as microglandular hyperplasia. Pure squamous cell carcinomas of the uterine corpus frequently are composed of well differentiated epithelium, which makes it possible to misinterpret them as non-neoplastic, and a similar phenomenon may occur in association with the squamous element in some adenosquamous carcinomas. Other entities that may be under-diagnosed are malignant lymphoma of the cervix, placental site trophoblastic tumor, myxoid leiomyosarcoma, endometrial stromal sarcoma with glandular differentiation, and mullerian adenosarcoma. Consideration of a variety of histological and cytological features should facilitate their interpretation. One recently described variant of adenocarcinoma of the fallopian tube that may be confused with the usually clinically benign female adnexal tumors of probable Wolffian origin is microfollicular endometrioid adenocarcinoma [1-7]. Ovarian tumors subject to misinterpretation that are reviewed herein include metastatic tumors with deceptively benign foci, endometrioid adenocarcinomas that may be misdiagnosed as sex-cord tumors, and cystic granulosa cell tumors that may be misinterpreted as follicle cysts. Finally, rare variants of malignant mesothelioma that may be under-diagnosed are briefly discussed as well.

Most of these rare tumors of the uterine cervix have been characterized only on the basis of patient history, pathology and histochemistry of the samples (e.g., colposcopic biopsy). Little progress has been made with few such tumors to identify potential molecular markers. Once validated, these markers would be valuable tools in early diagnosis, predicting prognosis and possibly as the targets of therapeutic intervention.

In addition to cervical cancer, the two main types of uterine malignancies are endometrial cancer and uterine sarcomas. Endometrial cancer (corpus and not otherwise specified uterine cancer) is the most common type of uterine cancer and the most common cancer of the female reproductive tract, accounting for approximately six percent of all female cancers. While the mortality rate has declined over the past 20 years among white women, it has remained stable among

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other racial and ethnic groups. Although the incidence of endometrial cancer is lower in African American women as compared to Caucasian women, the mortality rate is nearly twofold higher in this group. It is estimated that approximately $1.8 billion* is spent in the United States each year on the treatment of endometrial cancer (http://planning.cancer.gov/disease/Endometrial-Snapshot.pdf). Uterine sarcomas are rare malignancies that originate from muscular tissue and usually occur after menopause. Among the uterine sarcomas, two main types exist, i.e., leiomyosarcoma (origin from smooth muscle cells) and endometrial stromal sarcoma (connective tissue origin).

Rare tumors of the uterine cervix

A brief description of rare tumors of the uterine cerix is provided in the following section. In a few cases, potential markers have been identified, as summarized in Table 1. Examples of selected rare cervical carcinomas are illustrated in Figures 1 and 2.

Table 1. — *Potential markers of primary and metastatic tumors of the uterine cervix.*

Tumor types	Potential markers	Reference
Epithelioid leiomyosarcoma	Desmin, SMA, cytokeratin, S-100, HMB-45, vimentin, melan-A, CD68	[8]
Sarcomatoid squamous cell carcinoma (SSCC)	HPV16, phospho-retinoblastoma protein	[9]
Endocervical adenocarcinoma	No specific marker, identification based on histopathology	[10]
Adenoid basal carcinoma (ABC)	HPV16, cytokeratins 14, 17 and 19	[12, 13, 16]
Papillary squamous cell carcinoma PSCC)	HPV 6, 11 and 18	[17]
Transitional cell carcinoma (TCC)	Low-molecular-weight cytokeratin (LMW-CK, CAM5.2) and cytokeratin 7 (CK7)	[18]
Adenoid cystic carcinoma (ACC)	CK17, CK19, pancytokeratin, and 34β E12, but not for CK14, smooth muscle actin (SMA) or S-100	[19, 24]
Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix	EBV	[20, 21, 24-26]
Small cell neuroendocrine carcinomas (CNEC) of the uterine cervix	Neuron-specific enolase, synaptophysin, chromogranin A	[27-30]
Lymphoma-like lesion of the uterine cervix	EBV	[32, 33]
Primary non-Hodgkin's lymphoma of the uterine cervix	Lactate dehydrogenase (LDH), soluble interleukin-2 receptor (sIL-2R)	[34, 37]
Malignant melanoma of the uterine cervix	No specific marker, identified on histopathological examination	[41, 42]
Carcinosarcoma of the uterine cervix (CS)	No specific marker, identification based on histopathology (67)	[43, 44]
Adenoid basal carcinomas of the cervix	HPV 16, p16	[12, 13, 45-48]
Mesonephric adenocarcinomas of the uterine cervix	Cytokeratin 7, epithelial membrane antigen, CD15, vimentin	[22, 49]
Peripheral primitive neuroectodermal tumor of the cervix (PNET)	CD99	[50-52]
Sarcoma botryoides of the cervix	P53 mutation	[53, 54]
Adenosarcoma of the uterine cervix	No specific marker, identified on histopathological basis	[55]
Primary extrarenal Wilms' tumor of the uterus	No specific marker, identified on histopathological basis	[56]
Malignant schwannoma of the uterine cervix	No specific marker, identified on light microscopy	[57-61]
Glassy cell carcinoma of the uterine cervix (GCC)	HPV18, Her2/ neu	[62, 63]
Papillary squamotransitional cell carcinoma of the uterine cervix	No specific marker, identified on the basis of histopathology	[64]

Epithelioid leiomyosarcoma

Epithelioid leiomyosarcomas, arising from the uterine cervix, are extremely rare neoplasms. They are rare variants of smooth muscle cell tumors primarily characterized by the proliferation of round and polygonal epithelioid cells with eosinophilic cytoplasm intermingled with the malignant tumor component of smooth muscle origin. Although, leiomyosarcoma is one of the most common non-epithelial malignant neoplasms arising in soft tissue and organs, this malignancy is very uncommon in the uterine cervix. A diagnosis of epithelioid leiomyosarcoma of the uterine cervix can be performed by immunohistochemical methods using desmin, SMA, cytokeratin, S-100, HMB-45, vimentin, melan-A, and CD68 as biomarkers. Efforts for finding additional molecular markers for better diagnosis, prediction of prognosis, and optimal management strategies are being hampered by its extreme rarity [8].

Sarcomatoid squamous cell carcinoma

Sarcomatoid squamous cell carcinoma (SSCC) is usually identified in the oral cavity, pharynx, esophagus, and larnynx, but only rarely found in the female genital tract. The diagnosis of sarcomatoid carcinoma is primarily based on histological, immunohistochemical, and ultrastructural characteristics. Usually, a recognizable squamous cell carcinoma merges with a spindle cell component. Immunohistological and ultrastructural findings are indicative of epithelial differentiation and distinguish this lesion from sarcoma, but the distinction between sarcomatoid carcinoma and malignant mixed mullerian tumor (MMMT) is still under debate. SSCC

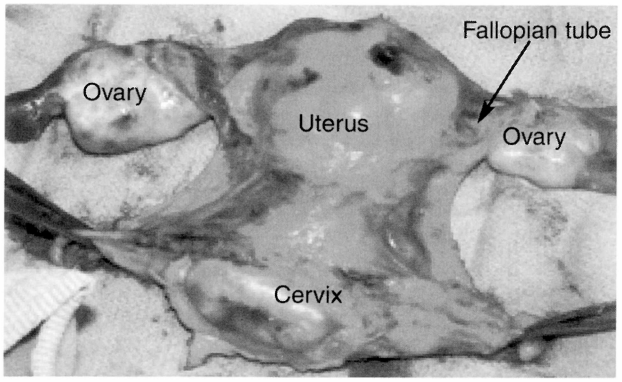

Figure 1. — Representation of cervical carcinomas including other parts of the reproductive tract.

is a histological variant of cervical cancer, with only four cases having been reported in the literature [9]. SSCC is characterized by biphasic components of sarcomatoid and neoplastic squamous cells, and has an uncertain pathogenesis. However, this malignancy was found positive for human papillomavirus (HPV) type 16 by PCR and in situ hybridization. Additionally, enhanced immunostaining for retinoblastoma (pRb) protein and decreased apoptosis compared with the usual squamous cell carcinomas have also been observed. The conclusions drawn from this limited series of reported cases indicate that SSCC is an aggressive malignancy. Its infrequent occurrence makes it difficult to identify novel molecular markers for this malignancy for a better diagnosis and effective disease management. To date, only 20 cases have been described [10].

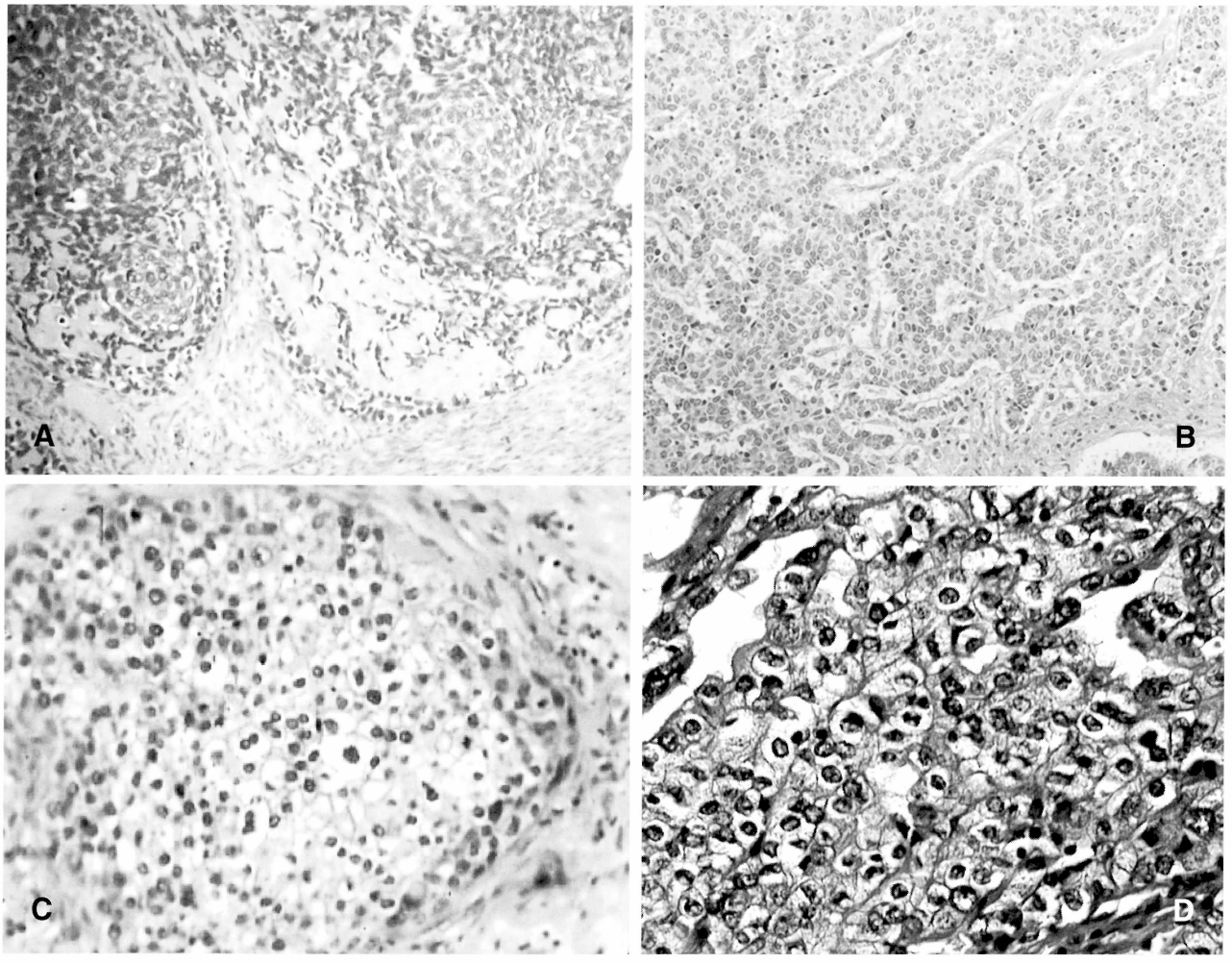

Figure 2. — Histoarchitecture of some rare cervical carcinomas (A) adenoid cystic cervical carcinoma, (B) clear cell carcinoma of the cervix, (C) cervical carcinoid tumor, and (D) glossy cell carcinoma of the cervix.

Endocervical adenocarcinoma

Mucin expression differs among benign endocervical lesions and adenocarcinoma in situ (AIS) and among endocervical and endometrial malignancies [11]. Mucin staining may be potentially helpful in differentiating these various glandular lesions of the cervix. When antibodies to MUC1, MUC2, MUC4, and MUC5AC were applied on endocervical adenocarcinomas (including adenosquamous carcinomas), endometrial carcinomas (endometrioid adenocarcinoma and adenosquamous carcinoma), adenocarcinoma in situ, glandular dysplasias, tubal metaplasias and microglandular hyperplasias, positive results were frequently observed.

Adenoid basal carcinoma

Adenoid basal carcinoma (ABC) of the uterine cervix is also very rare and its cell of origin is still ambiguous [12, 13]. Histological studies have shown that in ABC, the small round or oval cancer cell nests within the peripheral cell palisade and grows from the basal cell layer of the uterine cervix *in situ*. ABC is primarily characterized by the nested proliferation of basaloid cells. The tumor cells have shown no or very little nuclear atypia with low mitotic activity. The nests of cancer cells have shown infiltrating growth with no desmoplastic reaction in most of the reported cases. Immunohistochemically, these basaloid cells of ABC have shown a positive reactivity for cytokeratins 14, 17 and 19 and resemble the reserve cells of cervical squamous epithelium. This cancer type has a favorable prognosis that is clearly different from adenoid cystic carcinoma, which has a much poorer outcome [14]. In HPV testing, 67% of adenoid basal carcinomas were HPV-positive. Results of this study clearly demonstrated that the integrated high-risk HPV, in particular type HPV16, is associated with this uncommon type of cervical cancer [15]. ABC is usually found in postmenopausal women. An alternative name was proposed for this tumor; 'adenoid basal epithelioma' because of its excellent clinical outcome. This type of cervical cancer is almost always found as a latent asymptomatic lesion (up to 1 cm in the largest dimension) of a uterine cervix resected due to another cervical neoplasm, e.g., invasive carcinoma or cervical intraepithelial neoplasia (CIN). This carcinoma was first described by Baggish and Woodruff in 1966 [16]. Up to now, only a few cases of ABC have been reported in Japan [15].

Papillary squamous cell carcinoma

Papillary squamous cell carcinoma (SCC) of the uterine cervix is usually characterized by the presence of a papillary architecture with fibro-vascular cores and moderate to severe dysplasia, devoid of frank keratinization and koilocytic changes. Papillary SCC may be histologically delineated from the other rare variants of SCC with papillary features including verrucous (a low-grade variant of SCC) and condylomatous carcinoma and the recently recognized (squamo-) transitional cell carcinoma. Most of these cancer samples tested positive for HPV 16 and negative for HPV 6, 11 and 18 in a PCR enzyme-linked immunosorbent assay (PCR-ELISA). These findings suggest that papillary SCCs (unlike verrucous carcinoma) are similar with regard to risk factors to (squamo-) transitional and condylomatous carcinoma, and also suggest an etiologic role of HPV infection in at least some of these tumors. These findings suggest that papillary SCC is the only subtype among squamous/(squamo-) transitional carcinomas that is associated with high-risk HPV infection [17].

Transitional cell carcinoma

Transitional cell carcinoma (TCC) of the uterine cervix is an even rarer type of cervical carcinoma. This cancer usually has a papillary growth pattern that mimics carcinoma of the urothelial origin. These tumors grow as papillary elevated lesions in the intramucosal layer and do not invade the muscular layer. Microscopically, these tumors are composed of two different neoplastic subtypes: a) an AC component showing tubular structures lined by atypical cuboidal cells, and b) a TCC component showing papillary excrescence lined by atypical stratified cells with a vascular core papillary structure. In the AC component, cancer cells usually have sparse cytoplasm and hyperchromatic nuclei with frequent mitotic figures. The tumor cells in the TCC component show amphophilic cytoplasm and small, round nuclei with occasional mitotic figures. The TCC component is reminiscent of its urothelial origin. In immunohistochemical analyses, TCC samples have shown positive immunoreactivity for low-molecular-weight cytokeratin (LMW-CK, CAM5.2) and cytokeratin 7 (CK7) expressed in the tubular structure of the AC component and in the superficial epithelial layer of the TCC component. The lower epithelial layer of the TCC component was negative for LMW-CK (CAM5.2) and weakly positive for CK7. Cytokeratins 8 (CK8), and 19 (CK19) showed diffuse reactivity in both elements of AC and the whole layer of the TCC component. Carcinoembryonic antigen (CEA) was strongly positive at the luminal surface of the tubules in the AC component and the surface of the papillary TCC structure. A very faint or weakly positive reactivity to CEA was also observed in the whole TCC component. High-molecular-weight cytokeratin (HMW-CK, 34bE12), cytokeratin 20 (CK20) and HPV were negative in both components [18].

Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) of the uterine cervix is a rare and atypical variant of adenocarcinoma. ACC is also termed adenocystic carcinoma, cylindroma and cylindromatous adenocarcinoma. This carcinoma is most commonly found in the respiratory tract and salivary glands, accounting for less than 1% of all carcinomas of these organs. ACC of the uterine cervix constitutes 0.04-1.7% of all cervical carcinomas and represents 3.0% of all primary cervical adenocarcinomas. Cervical ACC shows a close similarity to ACC of the salivary glands. It is locally aggressive and capable of metastasis to other organs even in its early stage. In immunohistochemical analysis, these carcinomas stained positive for CK17, CK19, pancytokeratin, and 34β E12, but not for CK14, smooth muscle actin (SMA) or S-100. Generally, radiotherapy and chemotherapy are the first-line treatments because this neoplasm is seen most commonly in the elderly. The importance of differential diagnosis between ABC and ACC has been repeatedly emphasized. In addition to ACC, basaloid squamous cell carcinoma (BSCC), adenosquamous carcinoma (ASC), and adenoid basal hyperplasia

must also be considered in the differential diagnosis of ABC. It is especially important to carefully distinguish between ABC and ASC because ASC is a common death-causative disease of the uterine cervix, whereas ABC runs a much more benign course. It is known that ASC sometimes contains an ABC-like component. The adenoid structure of ABC can be misdiagnosed as a well-differentiated adenocarcinoma component of ASC, and *vice versa* [19].

Large cell neuroendocrine carcinoma

Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is a newly introduced category of the revised World Health Organization (WHO) classification. Twelve cases of neuroendocrine tumors (NETs) were reported by Albores-Saavedra *et al.* and were designated as carcinoid tumors of the cervix [20, 21]. Later, these tumors were classified into two categories; small cell carcinoma and carcinoid tumor. Although cervical small cell carcinomas are well-defined tumors with more than 250 reported cases, non-small cell NETs are much less common and have received little attention. Recently, the WHO launched its revised classification of tumors of the female genital organs [20-23]. According to the new classification, NETs of the uterine cervix are divided into four categories; a) carcinoid, b) atypical carcinoid, c) small cell carcinoma, and d) large cell neuroendocrine carcinoma (LCNEC). In this new WHO classification, cervical atypical carcinoid is described only as "a carcinoid with cytological atypia that exhibits increased mitotic activity (5-10 per high power fields)". Thus, although pulmonary atypical carcinoid is regarded as an intermediate-grade carcinoma, it is not clear whether cervical atypical carcinoids are intermediate-grade carcinomas or not [24].

Recently, immunohistochemical expression of HER-2/neu, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), estrogen receptor (ER), and progesterone receptor (PR) was analyzed in small cell and large cell neuroendocrine carcinomas (SCNECs and LCNECs) in 24 patients. Of these 24 cases, VEGF was expressed in 95.8% (n = 23), EGFR, HER-2/neu, and COX-2 expression were observed in eight (33.3%), ten (41.7%), and seven (29.2%) cases, respectively. ER and PR expression was present only in one (4.2%) and two (8.3%) tumors, respectively. HER-2/neu expression was significantly associated with survival in that the patients with negative HER-2/neu expression had significantly shorter survival than those with positive tumors [25]. Among 12 archival cases of LCNEC, integration of high-risk HPVs, in particular HPV16 and to a lesser extent HPV18, was found to be associated with this uncommon variant of cervical carcinoma [26].

Small cell neuroendocrine carcinomas

Small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix is a rare variant of cervical carcinoma with features of high aggressiveness [27-29]. SCNEC comprises approximately 0.8% of all cervical cancers. This tumor is very difficult to manage because it is often diagnosed at an advanced stage and prognosis is generally poor. SCNEC is a tumor most commonly seen in the lung, with characteristic histological findings, but it has been reported to develop in many other organs, including the stomach, rectum, breast, and ovary, and only rarely does it develop in the uterine cervix. SCNEC is known to metastasize to the lymph nodes at an early stage, resulting in a poor prognosis. Because of its poor prognosis and characteristic histopathological findings, it has been classified as an independent disease under the name small cell carcinoma [27]. However, the clinical and pathological features of SCNEC of the uterine cervix have not yet been fully elucidated because of the extreme rarity of this lesion.

Histopathologic findings show solid nests with a marked peripheral palisading pattern and rosette formation. Small tumor cells with scant cytoplasm demonstrate a very high nuclear/cytoplasm ratio and indistinct cell borders. The nuclei are round to oval and demonstrate increased but fine granular chromatin. Nucleoli are indistinct in all cases. Immunohistochemical studies of SCNEC have shown positive reactivity in 81.8% samples, each for neuron-specific enolase (NSE) and protein gene product, 72.7% for synaptophysin, 63.6% for chromogranin A, and 54.5% for neural cell adhesion molecules. All specimens were positive for at least one of the above markers. Due to the known poor prognosis, making an accurate diagnosis of SCNEC before treatment is of great significance, but often difficult [30].

Lymphoma-like lesions

The term "lymphoma-like lesion" was introduced by Young *et al.* in 1985, for inflammatory lesions of the lower female genital tract characterized by a benign reactive lymphoid hyperplasia simulating malignant lymphoma [31]. A lymphoma-like lesion of the uterine cervix is a benign reactive lymphoid hyperplasia associated with chronic cervicitis that may pose a problem in the differential diagnosis from malignant lymphoma. It is a rare entity and only about 22 cases have been reported in the world literature. The diagnosis of a lymphoma-like lesion is primarily based on the characteristic microscopic features. Immunohistochemical staining is usually not helpful in distinguishing this lesion from malignant lymphoma. No specific treatment is required for this lesion [32]. In a few cases, a silent EBV infection has been detected in serological tests. EBV DNA was demonstrated in nuclei of large lymphoid cells in endocervical curettage specimens by *in situ* hybridization, implicating an active EBV infection in this lesion. Therefore, in women with lymphoma-like lesions of the lower genital tract, an examination for EBV is recommended [33].

Primary non-Hodgkin's lymphoma

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of malignancies in terms of presentation, natural history and prognosis [34-39]. Lymph nodes are almost always the initial site of recognized disease and the gastrointestinal tract is the most frequent site of extra-nodal involvement. NHL frequently affects the uterine corpus, cervix, and vagina in cases of advanced disease. However, these organs are rarely the site of origin of this type of neoplasia. Primary NHL of the uterine cervix and upper vagina are rare in immunocompetent females; the literature has reported only a few cases in the last 20 years. The pathogenesis of these disorders is still matter of discussion and a standard treatment for NHL of the cervix and vagina has not been defined. However, the most accepted therapy is chemotherapy and/or radiotherapy, while surgery has been limited to diagnostic purposes only [34, 37]. In women with NHL of the uterine cervix, markedly elevated serum levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) were observed at the time of diagnosis. After three courses of combination chemotherapy, the serum levels of both LDH and sIL-2R returned within normal limits. This suggests that LDH and sIL-2R may be useful markers for this disease and its remission after treatment [34].

Malignant melanoma

Malignant melanoma is a relatively rare disease of the skin and mucous membranes, comprising only 1% of all cancers. Approximately 5% of malignant melanomas in women occur in the genitalia, with a predominant occurrence in the vulva and more rarely in the uterine cervix, uterus and ovary. The first case of malignant melanoma of the uterine cervix was reported by Johnston in 1989, who described it as a "melanotic sarcoma of the cervix uteri". The presence of melanin-cells in the uterine cervix was first reported by Cid [40]. A total number of 26 reported cases of primary melanomas of the uterine cervix had been diagnosed up to 1999. Vaginal bleeding was the main symptom in the majority of cases (83.0%), while only a few patients (8.3%) presented with vaginal discharge. In most cases, the macroscopic appearance was an exophytic cervical lesion varying in color from red, brown, gray, black, to blue [41, 42].

Carcinosarcoma

Carcinosarcoma (CS) is a rare neoplasm of a mixed epithelial and mesenchymal component. Occurrence of this tumor is well known in the esophagus, lungs, bladder, mammary glands, and uterine corpus. CS of the uterine cervix is much less common than its counterparts in the uterine corpus. Among all malignant uterine tumors, CS accounts for about 3%, the major site being the corpus. Cervical CS cases documented until now are limited to only 25 cases. The patients with CS were in the age range from 23 to 87 years, and 75% were > older than 50 years. CS of both the cervix and corpus has a poor prognosis due to its resistance to variable treatments. The incidence of metastasis in the parametrium is significantly higher in cervical CS as compared with epithelial malignancies. In CS lesions of the corpus, the carcinomatous component is usually adenocarcinoma, in contrast to CS of the cervix, where squamous cell carcinoma is equally common [43, 44].

Adenoid basal carcinomas

Adenoid basal tumors of the cervix have been designated as "adenoid basal carcinomas" (ABC). ABC are uncommon cervical lesions, composed of nests of uniform cells displaying basaloid, squamous, and glandular differentiation. There is lack of common consent among pathologists because some consider it an invasive carcinoma and others as an "epithelioma" due to the low-grade histological appearance and rarely documented malignant behavior. The most affected patients are asymptomatic postmenopausal women, usually diagnosed during a follow-up of abnormal cervicovaginal smears. The majority of adenoid basal epitheliomas and invasive carcinoma samples showed detectable HPV16 DNA in PCR analysis. In immunohistochemical analysis, most tumors have shown diffuse expression of p16, and on electron microscopy, tumor cells showed irregular nuclei, scanty cytoplasm and cribriform patterns, where gland-like structures were covered with basal lamina. Taken together, adenoid basal tumors seem to be high-risk HPV-related tumors that may comprise both a low-grade adenoid basal tumor, which can be designated as an epithelioma, and invasive carcinoma. Expression of p16 may be a useful molecular marker for these rare types of cervical carcinoma [12, 13, 45-48].

Mesonephric adenocarcinomas

Mesonephric (wolffian) adenocarcinomas of the female genital tract are infrequent. This rare type of adenocarcinoma is usually found in sites where the embryonic remnants of wolffian origin are usually detected, such as the uterine cervix, broad ligament, mesosalpinx, and ovary. These tumors frequently show combined patterns of retiform areas, ductal foci, and small tubules merging with solid sheets of cells with a sarcomatoid appearance. In immunohistochemical analyses, cancer cells were found diffusely positive for CK7, epithelial membrane antigen (EMA), and CD15, and focally positive for BerEP4 and vimentin. However, neoplastic cells showed a considerably higher immunoreactivity for CD10. Although the diagnosis of these tumors is difficult because of the lack of specific immunohistochemical markers, the expression of CD10 may be useful marker in establishing the diagnosis of mesonephric tumors. In addition, CD10 may also be a useful marker in the differential diagnosis between gynecologic clear cell carcinoma (always negative) and metastatic clear cell carcinoma of renal origin [22, 49].

Peripheral primitive neuroectodermal tumor

Primitive neuroectodermal tumor (PNET) is an extremely rare carcinoma of the cervix; until now, only eight cases have been described in the English literature. Light microscopic analysis showed small blue-stained cancer cells with tiny cytoplasm lying closely packed in sheets without rosette or gland formations. Cytoplasm of the tumor cells was clearly positive for glycogen on PAS staining. A number of epithelial and other markers were negative (keratin 7, 8, PAN-keratin, keratin 8.18, vimentin) in immunohistochemical analysis. Only CD99 showed a strong and extensive membranous immunoreactivity. Based on these findings, it is suggested that CD99 may be a useful molecular marker for the diagnosis PNET of the cervix [50-52].

Sarcoma botryoides

In the majority of cases sarcoma botryoides is often seen in the vagina during childhood. Infrequently, this disease arises in the cervix of the child. The pathological and clinical features of sarcoma botryoides of the vagina are well documented. However, only a few cases of similar tumors have been described in the uterine cervix thus far. Most patients with sarcoma botryoides of the cervix have presented with vaginal bleeding and/or some protrusion bodies from the introitus. In gross examination, the tumors are usually polypoid, smooth, glistening and focally hemorrhagic. Histological examination revealed the occurrence of a cambium layer and cells showing the features of rhabdomyoblasts in almost all the cases. The available reports suggest that sarcoma botryoides of the cervix in young women has a more favorable prognosis, unlike its counterpart in the vagina, which has a poor prognosis. Radical surgery combined with multi-agent chemotherapy has been used for the treatment of sarcoma botryoides in most patients [53, 54]. Although molecular markers for diagnosis of this disease are not well defined yet, a point mutation of the p53 tumor suppressor gene in exon 6 has been detected. Additionally, the p53 protein was also found to be over-expressed in more than half of the tumor cells. These data indicate that alterations in the p53 gene may play a role in the development and progression of sarcoma botryoides of the uterine cervix [54].

Adenosarcoma

Adenosarcoma (AS) of the cervix is of mullerian origin and is composed of malignant stromal and benign epithelial components. AS is a rare, biphasic tumor of the uterus and usually presents as a polypoid mass in the endometrial cavity. When found in the cervix, AS may be confused with benign cervical polyps clinically and pathologically. Mullerian AS with sarcomatous overgrowth in the cervix is extremely rare and an aggressive variant of AS. This variant contains obvious, high-grade sarcoma in addition to a low-grade form. Only 15 cases have been reported in the English literature. Its location in the cervix and the presence of heterologous elements are extremely infrequent. AS of the cervix with heterologous elements usually appears at the earliest stages of the reproductive lifespan in women, commonly characterized by a history of recurrent polyps. Accumulation of more cases is crucial for identification of appropriate molecular markers for the specific diagnosis of this rare malignancy of the uterine cervix [55].

Primary extrarenal Wilms' tumor

Wilm's tumors (WT) are the most frequently occurring primary retroperitoneal neoplasms in children. This malignancy is known to arise almost exclusively from the renal or juxta-renal region. The occurrence of true extra-renal Wilms' tumor (nephroblastomas) in other sites than the kidney is extremely rare, with a total 36 reported cases, of which only five cases were in the uterus. The most frequently noted extra-renal sites are the retroperitoneum, inguinal and sacrococcygeal/lumbosacral regions, spermatid cord, and testis. In the female genital tract, the occurrence of Wilms' tumor has been reported in the uterus, endocervix, and ovary as isolated case reports only [56].

Malignant schwannoma

Malignant schwannomas are also known as malignant peripheral nerve sheath tumors, neurogenic sarcomas, malignant neurilemmomas, and neurofibrosarcomas [57-61]. These are rare tumors originating from the neural sheath which are reported to occur most commonly in the major nerve trunks including the sciatic nerve, brachial plexus, and sacral plexus. Forty to fifty percent of patients diagnosed with malignant schwannomas have neurofibromatosis-1. Of those patients without neurofibromatosis who develop malignant schwannomas, 38% experience recurrence, and 16% develop metastasis, most commonly in the lung, soft tissue, bone, or liver. Malignant schwannomas of the uterine cervix are extremely rare, and only seven patients have been reported. All cases were treated by hysterectomy. Five-year survival for these patients was 53% and 10-year survival only 38%. Accordingly, malignant schwannomas of the uterine cervix are potentially aggressive neoplasms.

Glassy cell carcinoma

Glassy cell carcinoma (GCC) is a poorly differentiated variant of ASC of the cervix associated with an aggressive course and poor prognosis. Histological analyses of tumor biopsies have shown nests of cells with a granular or clear cytoplasm, displaying marked pleomorphism eosinophilic infiltrate in the stroma. Tumors showed a pure glassy cell

pattern and one showed glandular differentiation with intracellular and extracellular mucin. Cytology of GCC reveals characteristic features that differ from those of other carcinomas of the cervix, but may cause diagnostic confusion, possibly due to the lack of differentiation and low frequency of this tumor. GCCs may originate from multipotential stems or reserve cells that undergo early squamous differentiation. GCC tumors have shown a profile of cytokeratin expression similar to that of immature squamous cells of the cervix. In addition, GCC tumors have shown expression of intestinal-type mucin. Moreover, the presence of HPV 18 DNA has also been detected in some GCC neoplasms [62]. Most patients with this disease were treated with a combination of surgery, radiotherapy and chemotherapy, but showed a poor response. Immunohistochemical analysis revealed over-expression of Her2/neu in GCC, and that was correlated with more aggressive behavior and a worse clinical outcome. Although GCC runs an aggressive clinical course, early diagnosis may help in a more effective patient management. Therefore, identification of novel molecular markers is highly required for early diagnosis of GCC [63].

Papillary squamotransitional cell carcinoma

Papillary squamotransitional cell carcinoma (PSTCC) of the uterine cervix has features reminiscent of transitional cell carcinoma of urothelial origin. PSTCC is a poorly known subtype of cervical carcinoma with a propensity for late metastasis and local recurrence in spite of the fact that it could be histologically misinterpreted as CIN3 with a papillary configuration or as a squamous cell papilloma. This tumor is potentially aggressive, however, it presents at a more advanced stage or as an early invasive lesion, mainly in postmenopausal women [64].

Neuroendocrine tumors

Occurrence of neuroendocrine tumors in the female reproductive tract is rare, but if present, the uterine cervix is the most frequent site in the majority cases. Neuroendocrine tumors of the uterine cervix are also known as argyrophil cell carcinomas and now have been considered as a distinct clinical-pathological entity. Histologically, these carcinomas are usually poorly differentiated or undifferentiated. Several theories on the histogenesis of these tumors have been proposed including an origin from local neuroendocrine cells or from reserve cells. The latter hypothesis is supported by the fact that uterine neuroendocrine tumors frequently contain other histological components including adenocarcinoma and SCC or both. Diagnosis of these tumors is usually provided by immunohistochemistry and/or electron microscopy in addition to conventional light microscopy and Grimelius stain. The tumors are immunostained for an array of neuroendocrine markers and several ectopic hormones. Electron microscopic studies have revealed typical dense-core neurosecretory granules. Surgery, radiation therapy, and chemotherapy are the major therapeutic options for neuroendocrine carcinomas. However, optimal treatment methods have not yet been established because of the rarity of the tumor. Overall, patient prognosis is usually poor with most patients dying within one year from the diagnosis. A better survival could be achieved if patients were diagnosed at early stage [65].

Uterine lipoma

Lipoma of the uterus is a benign and rare tumor, with an estimated incidence of 0.12% to 0.3%, commonly affecting postmenopausal women. These tumors are composed of pure adipocytes with a typical yellow appearance and well-defined margins. Tumor areas are easily distinguishable from the surrounding myometrium by a thin capsule in contrast to leiomyomas. The origin and histogenesis of lipomatous tumors is not yet clear. However, some theories have been proposed to explain its origin and histogenesis, such as lipoblastic differentiation of misplaced embryonal rests, pluripotent cell migration along the uterine nerve and vessels, and metaplastic changes of stromal or smooth muscle cells of uterine fibroids. Immunohistochemical studies have supported the hypothesis of adipose metaplasia of smooth muscle cells of uterine fibroids. Immunoreactivity of adipocytes for vimentin, desmin, and actin as well as the lack of immunoreactivity to macrophage antigens such as CD68 and MAC387 confirm the hypothesis of direct transformation from smooth muscle cells. Ultrasonography allowed the identification of lipomatous tumors due to typical sonographic features. Complete absence of flow could be seen by color Doppler sonography. Lipomatous tumors of the uterus can be diagnosed with a high degree of certainty by ultrasonography in the presence of a homogeneously hyperechoic avascular mass [66].

Concluding remarks

Studying rare cancers provides us an opportunity to consider the reasons why these neoplasms are rare. Identification of host and modifiable factors may help us understand the etiology of miscellaneous primary tumors of the uterine cervix. Recently completed human genome sequence and HapMap might be useful in identifying intervention targets for these tumors in the future.

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