Introduction

The female genital tract is an infrequent site of metastasis. Diagnosis of metastatic extragenital malignancy to the cervix on cervical-vaginal smear is extremely rare. We performed review of the database with diagnosis of malignant neoplasm metastatic to the uterine cervix between 2006 and 2011. These examples of metastatic extragenital malignancies to the cervix are lymphoma, and two colorectal adenocarcinomas. In these cases, the cytopathological diagnosis was confirmed by histopathologic and immunohistochemical analysis examination of surgical specimens.

Case Report

Case 1
A 71-year-old woman was suffering from bilateral edema of the legs and a decreased amount of urine for one month. There was history of CAD (coronary artery disease) with regular follow up and medical control at a local medical department for 25 years. The patient presented at Chi-Mei Medical Center Hospital and clinical examination revealed the following results: WBC, $11.3 \times 10^3$/uL; RBC, $3.67 \times 10^6$/uL; Hb, 10.4 mg/dL; PLT, 291 $\times 10^3$/uL; creatinine, 1.61 mg/dL; CA-125, 41.8 IU/mL; and other levels within normal limits. A CT scan of the pelvis showed the following: hydronephrosis of the right kidney with poor perfusion, enlargement of the uterus with a rather homogenous infiltrative mass lesion, which invaded into the right adnexa and extended to the surrounding fatty planes of the pelvic floor, and lymphadenopathy over the right inguinal region. On transvaginal sonography, one cervical mass of about $5.3 \times 5.1$ cm with myometrial extension was shown. A Pap smear was performed, followed by cervical curettage and a biopsy of the right inguinal lymph node.

The cytology smear revealed normal-looking epithelial cells and many atypical lymphocytes with slight variation in size but no maturation. These atypical lymphoid cells had round to oval, notched nuclei, coarse chromatin and distinct nucleoli; no tangible body macrophage was found (Fig.1A). The section of endocervical curettage showed mainly blood clots and fragmented endocervical glands, as well as a fragment of stroma tissue infiltrated by atypical lymphoid cells. The architecture of the lymph node was almost totally effaced by monotonous infiltrating tumor cells with a starry-sky pattern, the infiltration being composed of medium-sized atypical lymphocytes with frequent mitosis. The surrounding adipose tissue was also involved. Immunohistochemically, these atypical lymphocytes express CD10, CD20, Bcl-6 and IgM (Fig.1B–E). The proliferation fraction as determined by Ki-67 immunostaining was almost at 100% (Fig.1F). Both the morphologic features and immunophenotype indicated a Burkitt’s lymphoma. The patient was treated with a combination of multiple drug therapy and high-dose chemotherapy, but the patient died 6 months after her initial presentation at our hospital.
Case2  A 77-year-old woman was diagnosed as having colorectal carcinoma in 2008. Pathologic diagnosis was mucinous adenocarcinoma with regional lymph node metastasis, the stage was pT4N1M0. Two year later, the patient had a cervical smear taken because of abnormal vaginal bleeding. Cervical smear examination showed absent tumor diathesis, high nuclear cytoplasmic ratio, marked hyperchromatism, cytoplasmic vacuolation, and overlapping cell cluster are suggestive of cancer cells probably of glandular type (Fig.2a.b). On the basis of these findings and the previous history of colorectal adenocarcinoma, these findings hinted at metastatic intestinal carcinoma. An abdominal and pelvic CT scan revealed expansile heterogenous mass in the cervix, 4.5x4.3x4.9cm in size. On microscopic examination section shows fragments of uterine cervical tissue. One of which exhibits extensively invasion of neoplastic tubuloglandular structures that express CK7-/CK20+, supportive of an adenocarcinoma of colorectal origin (Fig.2c-g). The patient was treated with a combination of multiple drug therapy and high-dose chemotherapy. Unfortunate, the patient died 10 months after her was diagnosed colorectal carcinoma metastasis to the uterine cervix.

Case3  A 62-year-old postmenopausal woman was admitted with the complaint of a newly recognized irregular vaginal mass that had been present for 6 months. She had sigmoid colon adenocarcinoma three years ago. She had a atypical glandular cells Pap test which was obtained six months ago and a normal mammography that was performed a years ago. On her Laboratory results including tumour markers were all considered as normal (Ca 125: 7,6 U/ml, Ca 19-9: 11,9 U/ml, Ca 15-3: 5,5 U/ml, CEA: 16,42). Histopathology revealed atypical epithelial cells with large vesicular nuclei and with prominent nucleoli infiltrating the vulva epithelium and stroma. Central necrosis and high mitotic activity was also reported in tumour clusters. CK-20 IHC examination of tumour cells revealed diffuse and strong cytoplasmic staining pattern. Contrarily, there was no CK-7 staining pattern observed in tumour cells. These features supportive of an adenocarcinoma of colorectal origin.

Discussion

Genital tract metastases of the gynecologic malignancies are common, however metastases arising from extragenital cancers are relatively rare. The most common extragenital tumours that metastasize through the genital tract are well defined in the literature, namely colon-rectum cancers (37%) and breast cancers (34%), followed by stomach, appendix and other uncertain primary cancers. Uterine involvement in non-Hodgkin’s lymphoma (NHL) is uncommon. Most patients experience abnormal bleeding and a large, bulky cervix. Cervical cytology is usually negative. So-called lymphoma-like lesions of the cervix were first described in 1985, differing from typical cervical lymphoma in superficial distribution, heterogeneity of lymphoid cells, and presence of inflammatory cells. Our case showed diffuse infiltration of monotonous lymphocytes with coarse chromatin in the cervix and uterine corpus. Therefore, the diagnosis of a lymphoma-like lesion was excluded.
Most NHL of the female genital organs are aggressive and treatment is delayed due to late diagnosis. The management of NHL in this location has not been well-defined due to the low incidence of the disease and limited discussion in the literature. The prognosis for patients with extranodal lymphomas is usually poorer than for those with nodal lymphomas due to inaccurate or delayed diagnosis. If diagnosed in the earlier stages, prognosis may be excellent compared to other gynecologic malignancies.

Lesions that masquerade primary gynecologic malignancies were noted where even pathologic Pap tests with high-grade lesions or atypical glandular cells have been reported as a result of gynecologic tract recurrence. Clinical presentations of the colo-rectal metastases to the lower genital tract are various and may be conflicting for a clinician. Metastatic lesions with unknown or suspected primaries warrant careful histopathologic assessment since management strategies and prognosis completely depend on accurate diagnosis. Within this perspective, many data has been accumulated on the use of immunohistochemicals (IHC) CK-7 and CK-20 to predict the origin of metastatic lesions, especially investing adenocarcinomas with unknown primaries. In general, lung, breast, endometrium, vagina and ovarian tissues contain CK-7 but not the colon.

In this extragenital metastatic neoplasms, as in other cases reported in literature, the patients had undergone cervical smear because of vaginal bleeding, even if Pap smear is considered a questionable maneuver in vaginal bleeding. Data from literature demonstrate that the most common extrauterine neoplasms with malignant cells in cervical smears are carcinoma of the ovary, adenocarcinoma of the gastrointestinal tract, the fallopian tube, and the breast. To our knowledge, the rarity of this occurrence could be due to the absence of clinical data referring to a previous history of malignant neoplasm and to misinterpretation of neoplastic elements on Pap smears as primary neoplasms of the cervix.

References
The cytology smear revealed normal-looking epithelial cells, many atypical lymphocytes with slightly variation in size but no maturation. These atypical cells had round to oval, notched nuclei, coarse chromatin and distinct nucleoli. No tangible body macrophage was found (Pap stain 400×). (B) Tumor cells express membrane IgM with light chain restriction (C) and B-cell associated antigens (CD20). (D) The expression of CD10 (E) and Bcl-6 point towards a germinal center origin for the tumor cells. (F) Ki-67 is more likely to be expressed in aneuploid tumors compared to diploid tumors, and it is associated with a high mitotic and high histology grade. This monoclonal antibody enables detection of Ki-67 in proliferating cell populations in routine paraffin sections. The antibody stains positive in nucleus of proliferation. (immunostain 400×)
Fig 2. a, b: Cervical smear examination showed absent tumor diathesis, high nuclear cytoplasmic ratio, marked hyperchromatism, cytoplasmic vacuolation, and overlapping cell cluster are suggestive of cancer cells. (Papanicolaou 10×, 40×)
Fig 2. c, d, e, f, g, h: Section shows fragments of uterine cervical tissue. One of which exhibits extensively invasion of neoplastic tubuloglandular structures (H.E 10×·40×) that express CK7-/CK20+, supportive of an adenocarcinoma of colorectal origin. Besides, tumor emboli are also discerned.