Int J Clin Exp Pathol 2015;8(1):1000-1006
www.ijcep.com /ISSN:1936-2625/IJCEP0002939

Case Report

Metachronous metastasis from the right colon adenocarcinoma to the vulva: an unusual report and literature review

Kexing Ren[1*], Xuelei Ma[1*], Feng Wang[1*], Fuchun Guo[1], Yu Jiang[2], Lei Liu[1]

[1]Department of Oncology and State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, China; [2]Department of Ultrasonography, West China Second Hospital, Sichuan University, Chengdu, China. [*]Equal contributors and co-first authors.

Received October 2, 2014; Accepted November 13, 2014; Epub January 1, 2015; Published January 15, 2015

Abstract: A 67-year-old woman who was presented to the gynecologist with a two-month history of heavy vaginal bleeding, after an excisional biopsy of vulvar mass, was diagnosed with the right colon adenocarcinoma metachronous metastasis to the vulva. Pathological examination preliminarily revealed by primary adenosquamous carcinoma of vulva. The original submitting pathologist and gynecologist were contacted to obtain the pathological and clinical information whenever possible, combining with a history of the right colon cancer, subsequently, which confirmed the diagnosis of vulvar metastatic adenocarcinoma. Distinguishing metastatic carcinoma from primary vulvar adenocarcinoma is crucial, since these carcinomas are different. Herein reports the second case of the right colon carcinoma presenting as a vulvar metastasis. This report also shows the differentiation, diagnosis and treatment of metastatic colon carcinoma and its metastatic route.

Keywords: Colon adenocarcinoma, metachronous metastasis, vulvar adenocarcinoma, differentiation, metastatic route, treatment

Introduction

The most common metastases for colon are the liver and the lung, whereas vulvar metastasis of colorectal cancer is an uncommon phenomenon and few literatures are reported [1-6], especially the right colon. Primary vulvar cancer comprises 2%-5% of the gynecologic malignancies, which is the fourth most common cancer of the female genital tract [2, 3]. Primary vulvar carcinomas are rare and are the most common type of a squamous cell (86%-90%) [2, 3]. Whereas very rarely adenocarcinoma accounts for 8%-9% and other histological types such as melanoma, clear cell carcinoma, endodermic sinus carcinoma, sarcoma botryoides, and basal cell carcinoma represent 5%-7% of the remaining histological types [5-7]. Therefore, primary vulvar adenocarcinoma is extremely rare, which should be considered metastatic from other tissue until proven otherwise [8-11]. Distinguishing metastatic carcinoma from primary vulvar adenocarcinoma is crucial, since these carcinomas is different. Costa described a case of vaginal metastasis from right colon cancer at first [1]. Herein report the second case of the right colon carcinoma presenting as a vaginal metastasis.

Case report

We report a 67-year-old women who after an excisional biopsy of a vulvar swelling was diagnosed with the right colon adenocarcinoma metachronous metastasis to the vulva. She noticed a firm and painless swelling in the right lower quadrant abdominal 1 years ago. The level of serum CEA antigen was elevated (16.54 ng/mL). Colonoscopy and pathological biopsy were performed in February 2013 and showed the evidence of colon cancer. PET/CT images displayed abnormal FDG hypermetabolic foci of lumps in colon and mesenteric lymph nodes and excluded other metastatic site of cancer (**Figure 1**). The patient was presented to the right hemicolectomy, lymphadenectomy and

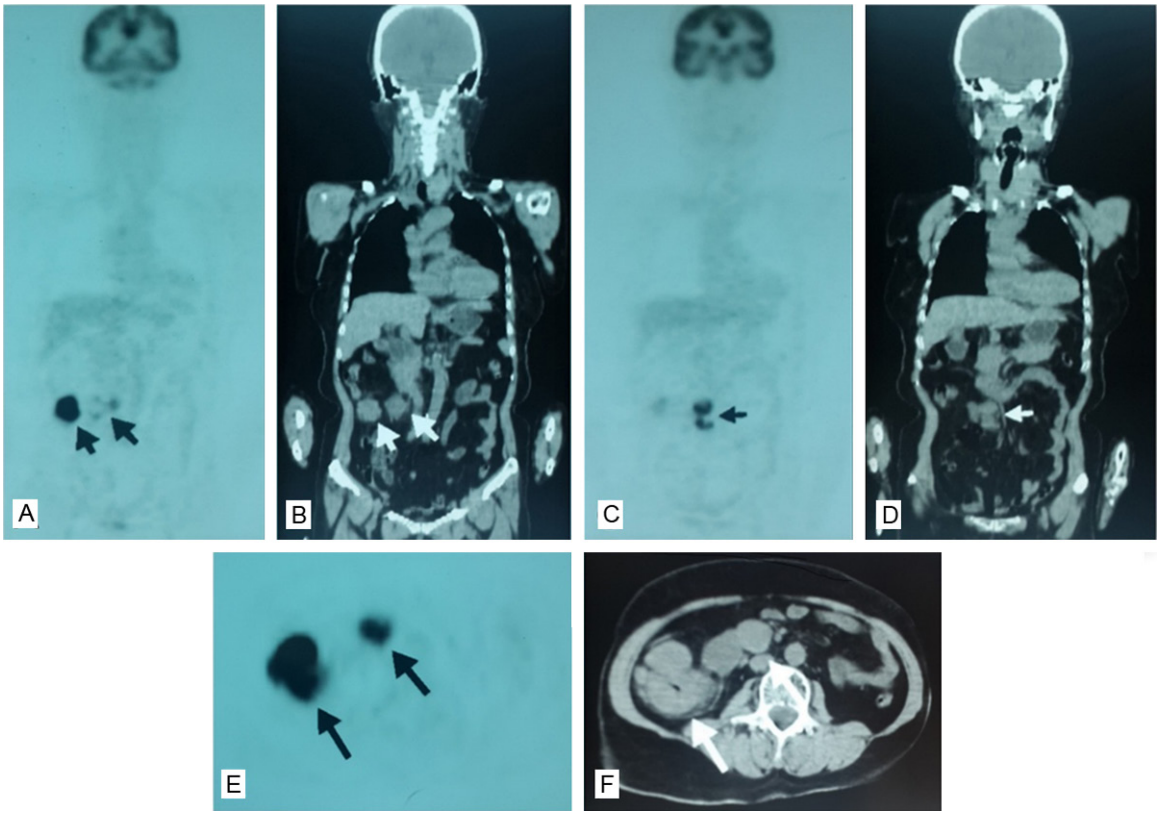

Figure 1. PET/CT images show hypermetabolic foci of a 5 cm mass and several swelling of mesenteric lymph nodes, compatible with a bowel obstruction.

exploratory operation, which showed no implants of metastatic tumor in pelvic and peritoneal cavity. The histopathologic examination comfirmed the diagnosis of low-differentiated colon adenocarcinoma in T3N2M0. After the resection, she was administrated by 12 courses of mFolfox-6 (oxaliplatin, 5-fu and leucovorin). The following routine surveillance CT scan indicated no evidence of tumor recurrence or distant metastasis.

The lady noticed a vulvar mass and presented with heavy vaginal bleeding and discomfort in lower abdomen in April 2014. There was no previous history of vaginal discharge or disfunction of bowel. Physical examination revealed that there was a soft abdomen without identifiable masses and a 3 cm external genitalia mass and swelling of bilateral painless inguinofemoral lymph nodes. Color Doppler ultrasonography revealed vulvar mass and enlargement of bilateral inguinofemoral lymph nodes. The palliative excision biopsy of vulva and inguinofemoral lymph nodes was applied to illuminating the diagnosis (**Figure 2A**). Initially, pathological examination revealed primary low-differentiated adenosquamous carcinoma of vulva (**Figure 2B**, **2C**). The original submitting pathologist and gynecologist were contacted for pathological and clinical information. Further examination of immunohistochemistry shows CK7 (-), CK20 (+++), EMA (+++) and the positive rate of Ki67 is 85% (**Figure 2D-F**). In addition, according to the retrospective study of pathological sections combined with a history of the right colon cancer, we confirmed the diagnosis of metastatic low-differentiation colon adenocarcinoma. Because of the negative of Ras gene mutation, she underwent four courses of the conbination treatment of Folfiri (irinotecan, 5-fu and leucovorin) with Cetuximab after wide local excision. An Enhanced-CT suggests that the swelling of vulva is obviously shrinked compare to that before the chemotherapy (**Figure 3**).

Discussion

Vaginal adenocarcinoma has been pathologically classified into two main types: diethylstilbestrol (DES)-related vaginal adenocarcinoma

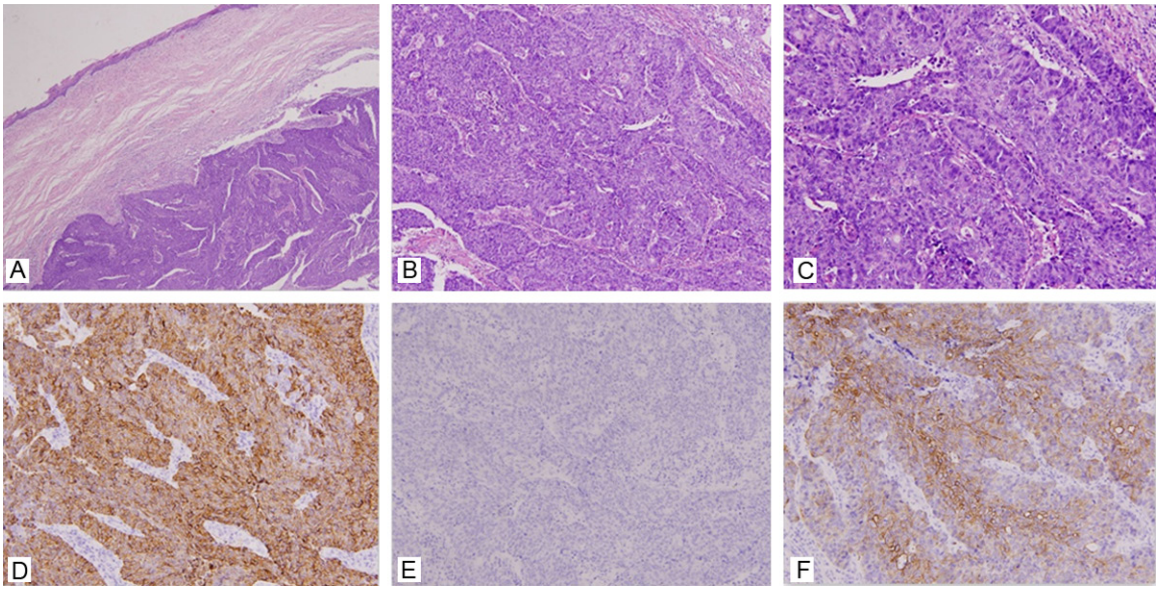

Figure 2. Photomicrographs demonstrating adenocarcinoma underlying vulvar epithelium; A. Low power view showing malignant cells underlying vulvar epithelium; B, C. High power view of the lesion shows low-differentiation malignant cells, which were histologically very difficult to confirm their origin (H&E 100, H&E 200); D. Positive immunostaining for EMA (+++); E. High power view demonstrating negative immunostaining for CK 7; F. Further examination of immunohistochemistry shows CK20 (+++).

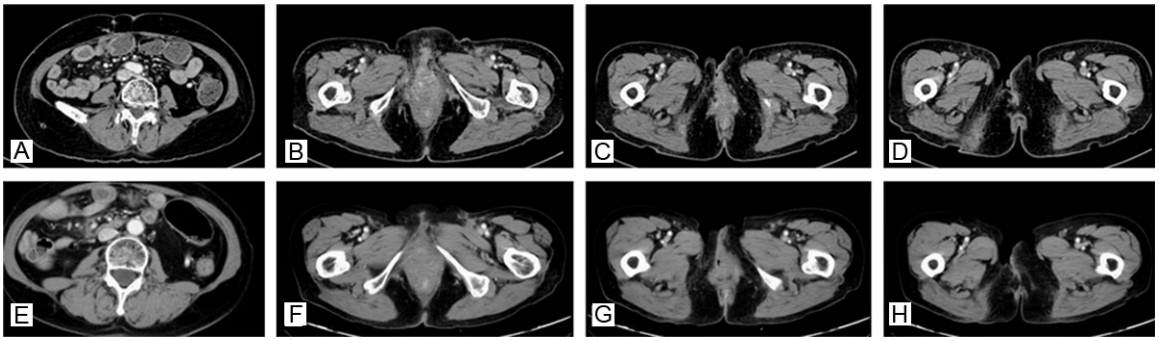

Figure 3. A-D. After the excision biopsy of vulva and inguinofemoral lymph nodes, CT shows that there is no cancer recurrence of primary foci and local swelling after resection; E-H. CT scan reveals that swelling of vulva is obviously shrinked than that before chemotherapy.

and DES-unrelated vaginal adenocarcinoma. Most primary vulvar adenocarcinomas occur in the Bartholin gland that is composed of columnar epithelium. Because of enlargement of the Bartholin gland in postmenopausal women and the rich lymphatic and vascular network contribute to the devolpment of malignancy [2]. Herbst and colleagues has first described adenocarcinoma of the vagina in women whose mother with pregnancy had been treated with DES in 1971 [12, 13]. Over the last 30 years, we have established the theory that there is a direct correlation between pregnant women within the context of DES exposure and the subsequent development of vaginal adenocarcinoma, especially during the first 16 weeks [12, 14]. DES-related vaginal adenocarcinoma is pathologically classified as clear cell variant [15]. DES-unrelated vaginal adenocarcinoma is extremely infrequent and the mechanism of oncogenesis have not been clarifid [12]. Some cases support the theory that vaginal adenocarcinoma derive from areas of vaginal adenosis, Wolffian rest remnants, foci of endometriosis and periurethral glands [15, 16]. A part of histopathological subtypes have been recognized, such as clear cell, endometrioid, enteric-type, mucinous, and serous type [17, 18].

Adenocarcinoma tends to typically presenting on the proximal third anterior wall of vagina which correspond to the most frequent place of adenosis [16]. The structure of these tissues have been described as ulcerated, polypoid, plaque-like, or papillary lesions [16]. Additionally, vaginal adenosis can develop as a process of transformation after HVP infection or trauma including surgry [17]. Primary vaginal adenocarcinoma of enteric-type is extremely rare and not association with DES exposure, which and often pose diagnostic problems and must be distinguished from adenocarcinomas originating in the gastrointestinal tract. The precise mechanism of the development of enteric type has not been clarified. Nevertheless, since the lower vagina is derived from the urogenital tract, it may arise from foci of gastrointestinal metaplasia from cloacal remnants [19, 20] and mesonephric ducts rest [21]. Some literatures report that enteric neoplasm may possible develop from the female genital tract, such as Mqllerian origin, foci of endometriosis and urogenital tract [19, 21].

Recently, some cases reported primary vaginal adenocarcinoma with differentiation of enteric-type [22-24]. Despite consideration of cancerous origin, the main clinical issue is to establish a method of pathology to different primary enteric adenocarcinoma of vulva and metastatic colon cancer. It is well-known that the combined detention of CEA, CK20 and CK7 has been proposed as an aid to differentiation [19, 25]. CK-20 is a low molecular weight cytokeratin extract from intestinal epithelium, which is a consistent expression in primary or metastatic colorectal carcinomas [22, 25]. CK-7 is detected in most transitional and glandular epithelia [26], which is also expressed on lung adenocarcinomas, breast and specific subtypes of ovarian cancer, but not colon malignancy [22, 27]. CK 20+/CEA+/CK7- is the greatest proportion in colorectal carcinomas [17, 19]. The CK7+/CK20-tumors include ovary, lung, thyroid, salivary gland, endometrium, breast, and mesothelioma [28]. However, Primary vaginal adenocarcinoma of enteric-type shows a flexible situation. Some case shows the coexpression of CK7 and CK20 [19], or positive for CK7 and CEA and negative for CK20 [24]. It is to be observed that the detection of CDX2 provides a novel method of confirming malignancies. CDX2 is a nuclear transcription factor expressed in enteric-type adenocarcinoma, which shows a strong nuclear positivity, characteristic of enteric differentiation and more specific than CK20 [21, 25]. Although there are some exceptions, most tumors of the large bowel are typically CK7-/CK20+/CDX2+/CEA+ [24], most tumors of primary enteric adenocarcinoma of vulva are CK7+/CK20+/CDX2+/CEA+, and primary non-enteric adenocarcinoma of vulva may just shows CK7+/CK20-/CDX2-/CEA- [19, 24, 29]. Although the clinical and pathological investigations showing no evidence of metastases, it is possible to exclude primary vaginal cancer and confirm the diagnosis according to pathological and clinical information combined with a history of the right colon cancer. In our opinion, immunohistochemical analysis, retrospective analysis of past history and extensive radiological investigation, including PET scan may play a role in detecting occult cancers.

In addition, how do these cancer cells transfer to the vulva? Metastatic adenocarcinoma of vulva may originate from the genital tract such as ovary, endometrium or cervix in approximately 65% of cases, which are more common than extragenital cancers [10]. After genital neoplasm, the primary lesions arise from the breast, kidney, gastrointestinal tract or pancreas [15]. These metastatic malignancies often affect the ovary [9], and the vulva is the less frequent site for metastatic deposits [5]. It has been supposed that because of the rich vascular and lymphatic network of superfluous ovary and intrinsic ovarian tissue metabolic features, the ovaries are suitable for malignant cell implantation and development of metastases [30, 31]. On the other hand, the other reproduction organs seem resistant to metastasis [32]. Approximately 6-7% of adnexal masses which are suspicious for an ovarian neoplasm will be confirmed to be metastatic lesion [30]. Primary colon cancer is one of the commonest causes of metastases, accounting for nearly 32.2% [31]. Spreading to the ovaries is the cue for an ominous progression of colorectal carcinoma and has been supposed to be a rapid progression and relative chemo-resistance [31, 33]. Malignant cells can also directly spread from adjacent tumor from rectal carcinomas, cervical, ovary, endometrial, bladder, which may result in the vast majority of vulval and vaginal metastases. These metastases in the upper third anterior wall of vagina may derive from the upper genital tract, however, in the lower third and posterior wall, the primary focuses may

originate from the digestive tract [34]. Compared to direct invasion, when malignant cells transfer to the vulva from preceding ovarian metastases, they maybe secondary to lymphatic spread [34]. Subsequent to obstruction of retroperitoneal lymphatics, disseminattion of neoplasm may be caused by lymph stasis and retrograde lymphatic diffusion [33]. Cancer emboli in the enlargement lymph nodes may support the concept of lymphatic obstruction and spread. More interestingly, whether or not metastases are involved in the ovaries, the mechanism of metastasis may be through the hematogenous [34, 35]. What's more, approximately 80% metastases occur within the first 3 years after surgical removal of the primary cancer [34]. Sometimes, surgery may be a potential source of metastasis and contribute to dissemination of exfoliated tumor and hematogenous metastasis [35]. We consider that this patient present with metastases restricted to the vulva, which seems to be related to transvascular metastasis.

Currently, there are no official recommended treatments and management outcome for metastatic adenocarcinoma of vulva, which is still open to be discussions and needs more efforts to address it. The management of metastatic diseases is dependent on the underlying primary neoplasm and the amount of secondary malignancy. What's more, there is no reference to surgical intervention of this rare lesion since it is frequently associated with widespread [9]. Nevertheless, when patients with a lesion in the vulva present with serous symptom, the primary and metastastic foci is amenable to be properly treated. Aggressive and competitive executive maybe performed in an attempt to improve symptoms and reduce local recurrence. The desired results are to obtain negative incised margins without causing distribution and disturbances to neighboring tissue or organs [18]. In addition to surgery, It is certainly worthwhile presenting comprehensive therapeutic options to the patients; for instance, radiotherapy, chemotherapy and biological treatment used individually or in combination. Therapeutic agents, such as 5-fu, Folfiri and Folfox combined with Cetuximab or Avastin , can be adopted to abort the metastatic cascade and improve survival [17, 33]. This woman presented with the negative of Ras gene mutation, therefore, she was given the combination treatment of Folfiri with Cetuximab after wide local excision. Moreover, for the better tumor local control, the patients should be given the radiotherapeutic doses of 70-75 Gy to the vaginal tumor, 50 Gy to the lateral parametrium, and 65 Gy to the medial parametrium.

In conclusion, there are no proposed standard diagnosis and therapeutic methods for metastatic colon carcinoma of vulva. Due to the rare frequency of this disease, it is difficult to perform large-scale laboratory experiments and controlled prospective clinical studies to illuminate this disease. Nevertheless, it is certainly worth the effort of calling for retrospective study like this paper, which may open up a new scope to solve this complicated problem.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lei Liu, Department of Oncology and State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China Medical School, Sichuan University, Guoxue Road No. 37, Chengdu 610041, Sichuan, People's Republic of China. Tel: 86-028-85422589; Fax: 86-028-85582944; E-mail: liuleihx@gmail.com

References

[1] Costa SRP, Antunes RCP, Abraão AT, Silva RM, Paula RP, Lupinacci RA. Single vaginal metastasis from cancer of the right colon: case report. Einstein 2009; 7: 219-21.

[2] Fuh KC, Berek JS. Current management of vulvar cancer. Hematol Oncol Clin N Am 2012; 26: 45-62.

[3] Marchal F, Leroux A, Hoffstetter S, Granger P. Vaginal metastasis revealing colon adenocarcinoma. Int J Colorectal Dis 2006; 21: 861-862.

[4] Gadducci A, Cionini L, Romanini A, Fanucchi A, Genazzani AR. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. Crit Rev Oncol Hematol 2006; 60: 227-241.

[5] Chagpar A, Kanthaqn SC. Vaginal metastasis of colon cancer. Am Surg 2001; 67: 171-172.

[6] Perez CA, Gersell DJ, McGuire WP, Morris M, et al. Principles and Practice of Gynecologic Oncology. In: Lippincott, Williams, and Wilkins, editors. 3rd edition. Philadelphia, PA: 2000. pp. 811-40.

[7] Cantisani V, Mortele KJ, Kalantari BN, Glickman JN, Tempany C, Silverman SG. Vaginal metastasis from uterine leiomyosarcoma:

magnetic resonance imaging features with pathological correlation. Comput Assist Tomogr 2003; 27: 805-809.
[8] Allard JE, McBroom JW, Zahn CM, McLeod D, Maxwell GL. Vaginal metastasis and thrombocytopenia from renal cell carcinoma. Gynecol Oncol 2004; 92: 970-973.
[9] Piura B, Yanai-Inbar I, Rabinovich A, Zalmanov S, Goldstein J. Abnormal uterine bleeding as a presenting sign of metastases to the uterine corpus, cervix and vagina in a breast cancer patient on tamoxifen therapy. Eur J Obstet Gynecol Reprod Biol 1999; 83: 57-61.
[10] O'Donovan EJ, Narayanan P, Sohaib SA. Nonsquamous Malignant Disease of the Vagina. Abdom Imaging 2013; 2183-2192.
[11] Saitoh M, Hayasaka T, Ohmichi M, Kurachi H, Motoyama T. Primary mucinous adenocarcinoma of the vagina: possibility of differentiating from metastatic adenocarcinomas. Pathol Int 2005; 55: 372-375.
[12] Frank SJ, Deavers MT, Jhingran A, Bodurka DC, Eifel PJ. Primary adenocarcinoma of the vagina not associated with diethylstilbestrol (DES) exposure. Gynecol Oncol 2007; 105: 470-474.
[13] Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971; 284: 878-881.
[14] Ditto A, Martinelli F, Carcangiu ML, Hanozet F, Solima E, Barisella M, Cerrotta A, Raspagliesi F. Incidental diagnosis of primary vaginal adenocarcinoma of intestinal type: a case report and review of the literature. Int J Gynecol Pathol 2007; 26: 490-493.
[15] Bozacı EA, Atabekoğlu C, Sertçelik A, Ünlü C, Ortaç F. Metachronous metastases from renal cell carcinoma to uterine cervix and vagina: case report and review of literature. Gynecol Oncol 2005; 99: 232-235.
[16] Hacker NF, Eifel PJ, van der Velden J. Cancer of the vagina. Int J Gynecol Obstet 2012; 119: S97-S99.
[17] Paczos TA, Ackers S, Odunsi K, Lele S, Mhawech-Fauceglia P. Primary vaginal adenocarcinoma arising in vaginal adenosis after CO2 laser vaporization and 5-fluorouracil therapy. Int J Gynecol Pathol 2010; 29: 193-196.
[18] Staats PN, McCluggage WG, Clement PB, Young RH. Primary Intestinal-type Glandular Lesions of the Vagina: Clinical, Pathologic, and Immunohistochemical Features of 14 Cases Ranging From Benign Polyp to Adenoma to Adenocarcinoma. Am J Surg Pathol 2014; 38: 593-603.
[19] Lee SE, Park NH, Park I, Kang SB, Lee HP. Tubulo-villous adenoma of the vagina. Gynecol Oncol 2005; 96: 556-558.
[20] Fox H, Wells M, Harris M, McWilliam LJ, Anderson GS. Enteric tumours of the lower female genital tract: a report of three cases. Histopathology 1988; 12: 167-176.
[21] Dzikonski M, Raber G, Kohly A. Gartner's duct carcinoma of vagina in pregnancy: a case report. Zentralb Gynako 1979; 101: 1595Y9.
[22] Mudhar HS, Smith JH, Tidy J. Primary vaginal adenocarcinoma of intestinal type arising from an adenoma: case report and review of the literature. Int J Gynecol Pathol 2001; 20: 204-209.
[23] Yaghsezian H, Palazzo JP, Finkel GC, Carlson JA, Talerman A. Primary vaginal adenocarcinoma of the intestinal type associated with adenosis. Gynecol Oncol 1992; 45: 62-65.
[24] Peña-Fernández M, Abdulkader-Nallib I, Novo-Domínguez A, Turrado-Sánchez EM, Brea-Fernández A, Sebio-Lago L, Ruíz-Ponte C, Cameselle-Teijeiro J. Vaginal tubulovillous adenoma: a clinicopathologic and molecular study with review of the literature. Int J Gynecol Pathol 2013; 32: 131-136.
[25] Moll R, Zimbelmann R, Goldschmidt MD, Keith M, Laufer J, Kasper M, Koch PJ, Franke WW. The human gene encoding cytokeratin 20 and its expression during fetal development and in gastrointestinal carcinomas. Differentiation 1993; 53: 75-93.
[26] Moll R, Franke WW, Schiller DL, Geiger B, Krepler R. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 1982; 31: 11-24.
[27] Ramaekers F, van Niekerk C, Poels L, Schaafsma E, Huijsmans A, Robben H, Schaart G, Vooijs P. Use of monoclonal antibodies to keratin 7 in differential diagnosis of adenocarcinomas. Am J Patho 1990; 136: 641-55.
[28] Feldman AL, Eunhee SY. Rosai and Ackerman's Surgical Pathology. JAMA 2012; 307: 201-201.
[29] Cobanoglu U, Ozoran Y. Tubulo-villous adenoma vagina. Case report. Aegean J Pathol 2004; 1: 47-9.
[30] Kim DD, Park IJ, Kim HC, Yu CS, Kim JC. Ovarian metastases from colorectal cancer: a clinicopathological analysis of 103 patients. Colorectal Dis 2009; 11: 32-38.
[31] Kuijpers AM, Mehta AM, Aalbers AG, van Driel WJ, Boot H, Verwaal VJ. Treatment of ovarian metastases of colorectal and appendiceal carcinoma in the era of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol 2014; 40: 937-942.
[32] Zhang YC, Zhang PF, Wei YH. Metastatic carcinoma of the cervix uteri from the gastrointestinal tract. Gynecol Oncol 1983; 15: 287-290.
[33] Goéré D, Daveau C, Elias D, Boige V, Tomasic G, Bonnet SM, Pocard C, Dromain M, Ducreux P, Lasser D, Malka D. The differential response

to chemotherapy of ovarian metastases from colorectal carcinoma. Eur J Surg Oncol 2008; 34: 1335-1339.

[34] Parikh JH, Barton DP, Ind TE, Sohaib SA. MR imaging features of vaginal malignancies 1. Radiographics 2008; 28: 49-63.

[35] Sleeman JP, Nazarenko I, Thiele W. Do all roads lead to Rome? Routes to metastasis development. Int J Cancer 2011; 128: 2511-2526.