CASE REPORT

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Difficulties of clinical and histopathological diagnosis in advanced vulvar clear cell carcinoma

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Abstract

Clear cell carcinoma (CCC) of the female genital tract usually arises in the ovary, endometrium, cervix and vagina. A rare site for CCC is the vulva, and moreover even rarer are the cases involving the Bartholin gland. A 54-year-old female was admitted for a 1.5×2 cm tumor at the level of the right Bartholin gland. The magnetic resonance imaging (MRI) exam revealed enlarged inguinal, pelvic and para-aortic lymph nodes but no other primary tumor. Microscopic examination revealed CCC. The tumor was positive for cytokeratin 7 (CK7), paired-box 8 (Pax8), napsin A and vimentin, negative for estrogen receptor (ER), progesterone receptor (PR), calretinin, cluster of differentiation 10 (CD10), carcinoembryonic antigen (CEA), p16 and p63. Also, p53 was expressed in 30–40% and Ki67 in 70% of the malignant cells. Given the clinical, imagistic, histological and immunohistochemical features of the tumor, we concluded that the tumor is a CCC of the Bartholin gland. Aim of the study is to signal a rare case of CCC of Bartholin gland. Since there are only two other cases reported in literature, the natural history and prognosis of the disease is not known, also there are no therapeutic guidelines regarding this rare tumor so appropriate treatment is uncertain. Therefore, it is important that new cases are reported for a better understanding of this rare condition. Bartholin gland carcinoma is a pathology quite rarely encountered in practice. The positive diagnosis is eminently histological and immunohistochemistry. Bartholin gland CCC is an extremely rare diagnosis with, to our knowledge, only two other cases reported in literature, but with a potential aggressive clinical behavior and poor outcome.

Keywords: clear cell carcinoma, Bartholin gland carcinoma, lymph nodes, immunohistochemistry.

Introduction

Vulvar cancer is a disease of elderly women, especially over 70 years of age, but can also occur in pre and post menopause [1–7]. Etiopathogenic, vulvar cancer depends on the age of the woman and can be divided into two groups. Vulvar cancer occurring in women less than 55 years old has a history of sexually transmitted diseases, infection with human papilloma virus (HPV), herpes simplex virus (HSV), smokers, women with low socio-economic level, just as in cervical cancer [8, 9]. Late-onset vulvar cancer in women over 55 years old has no history of sexually transmitted infections and is not smoker; HPV is present in 15% of cases [8, 10]. Lichen sclerosus can be a precursor lesion to vulvar cancer in older women [11]. Untreated vulvar intraepithelial neoplasia (VIN) can progress to invasive cancer within an average of four years [12, 13].

With primary neoplasm of the Bartholin gland representing just 2–7% of vulvar cancers, primary carcinomas have a very low incidence of just 0.2–1 per 1 000 000 women [14, 15]. The mean age at diagnosis for primary neoplasms of the Bartholin gland is 50–60 years with a range of 14–85 years [14, 16].

Bartholin cysts and abscesses are unusual after menopause and should raise the suspicion of a neoplasm. Bartholin gland enlargement in women over 40 years old, recurrent cysts and abscesses require biopsy and ablation. Excision of Bartholin gland cysts in women over 40 years old can exclude neoplasm in this location. Some authors suggest that morbidity on gland excision cannot be justified by this rare form of cancer. They recommend incision, cyst drainage, and biopsy of the cyst wall [17]. Bartholin gland carcinoma disseminate into the inguinal nodes and pelvic lymph nodes and into the ischiorectal fossa.

Therapy consists of radical partial vulvectomy with

inguinal lymphadenectomy. Preoperative chemoradiotherapy is recommended to avoid extensive surgery. Postoperative chemoradiotherapy can reduce local recurrence. In advanced stages, chemoradiation help lower tumor. Surgical treatment results in major anatomical changes and psychosocial negative effects.

Early detection of neoplasia and conservative surgical therapy can improve the psychosocial impact, taking into account issues, such as anxiety, depression, decreased self-esteem, and negative perception of one's own image.

Clear cell carcinoma (CCC) of the female genital tract usually arises in the ovary, endometrium, cervix and vagina. In such circumstances, it is useful to make a differential diagnosis with benign or malignant ovarian tumors, endometrial hyperplasia with carcinogenic potential [18–20]. A rare site for CCC is the vulva, and moreover even rarer are the cases involving the Bartholin gland.

From all the histological types of Bartholin gland carcinomas, an extremely rare type is the CCC with only two cases reported in literature [21, 22]. Considering the fact that CCC's misdiagnosis is one of the most common errors in gynecologic pathology, immunohistochemistry (IHC) with a wide panel of antibodies is used to distinguish among different primary tumors, exclude other primary CCCs elsewhere, especially the ovary and kidney [21].

Aim

The aim of the study is to signal a rare case of CCC of Bartholin gland. Since there are only two other cases reported in literature, the natural history and prognosis of the disease is not known, also there are no therapeutic guidelines regarding this rare tumor so appropriate treatment is uncertain. Therefore, it is important that new cases are reported for a better understanding of this rare condition.

Case presentation

A 54-year-old post-menopausal female patient was admitted to "Polizu" Clinical Hospital, "Alessandrescu–Rusescu" National Institute for Healthcare of Mother and Child, Bucharest, Romania, in February 2017, with a suspicion of recurrent Bartholinitis. She had an unremarkable personal and family history with the exception of two repeated right Bartholin gland abscessed in the past year, that were treated with surgical incision and drainage.

On examination, at the level of the right Bartholin gland, there was a painless, firm, 1.5×2 cm tumor, protruding through the former incised cyst wall (Figure 1A). No Bartholin's gland remnants could be observed as the area was entirely occupied by the tumor. Inguinal examination revealed bilateral enlarged, fixed lymph nodes with a maximum diameter of 6 cm on the right and 3 cm on the left.

The transvaginal ultrasound (US) scan revealed normal internal genital organs in postmenopausal involution. A magnetic resonance imaging (MRI) of the pelvis and abdomen was performed and revealed a 25/15 mm tumor at the level of the right major labia and multiple enlarged inguinal, pelvic, and also para-aortic lymph nodes (Figure 1B). The rest of the abdominal organs appeared normal and there was no sign of ascites or peritoneal carcinomatosis.

A tumor and right inguinal lymph node biopsy were taken and microscopic examination revealed clear tumor cells with well-defined membranes predominantly arranged in diffuse sheets without any architectural details, characteristic for the solid pattern of CCC. Thin fibrous septae were present between the solid tumor regions (Figure 2, A and B).

IHC showed the tumor and lymph node metastasis were negative for estrogen receptor (ER), progesterone receptor (PR), calretinin, cluster of differentiation 10 (CD10), carcinoembryonic antigen (CEA), p16, and p63. The biopsies were diffusely positive for cytokeratin 7 (CK7), paired-box 8 (Pax8), napsin A (Figure 2, C, D and F) and had areas of vimentin-positive cells (Figure 2E). Also, p53 was expressed in 30–40% and Ki67 in 70% of the malignant cells (Figure 2, G and H).

This tumor was classified as a stage IV B (pT1b N3 M1) due to the inguinal, pelvic and para-aortic lymph nodes metastasis. Given the advanced stage of the disease, there was no indication for primary surgical treatment. Since the vulvar tumor was not removed, no histological remnants of normal Bartholin gland tissue were found. The patient underwent four cycles of platinum-based chemotherapy with initial partial response. Due to gastrointestinal grade III toxicity and poor performance status, the treatment was stopped.

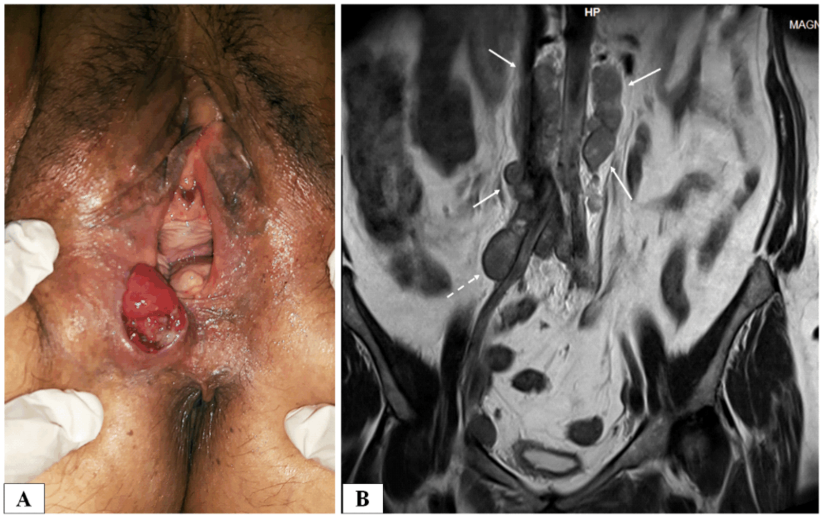

Figure 1 – ***(A) Photography of the vulva, with a 1.5×2 cm tumor growing from the former Bartholin gland; (B) Coronal T2-weighted MRI exam of the lower abdomen and pelvis showing enlarged para-aortic lymph nodes (arrows) and enlarged right iliac lymph nodes (dashed arrow). MRI: Magnetic resonance imaging.***

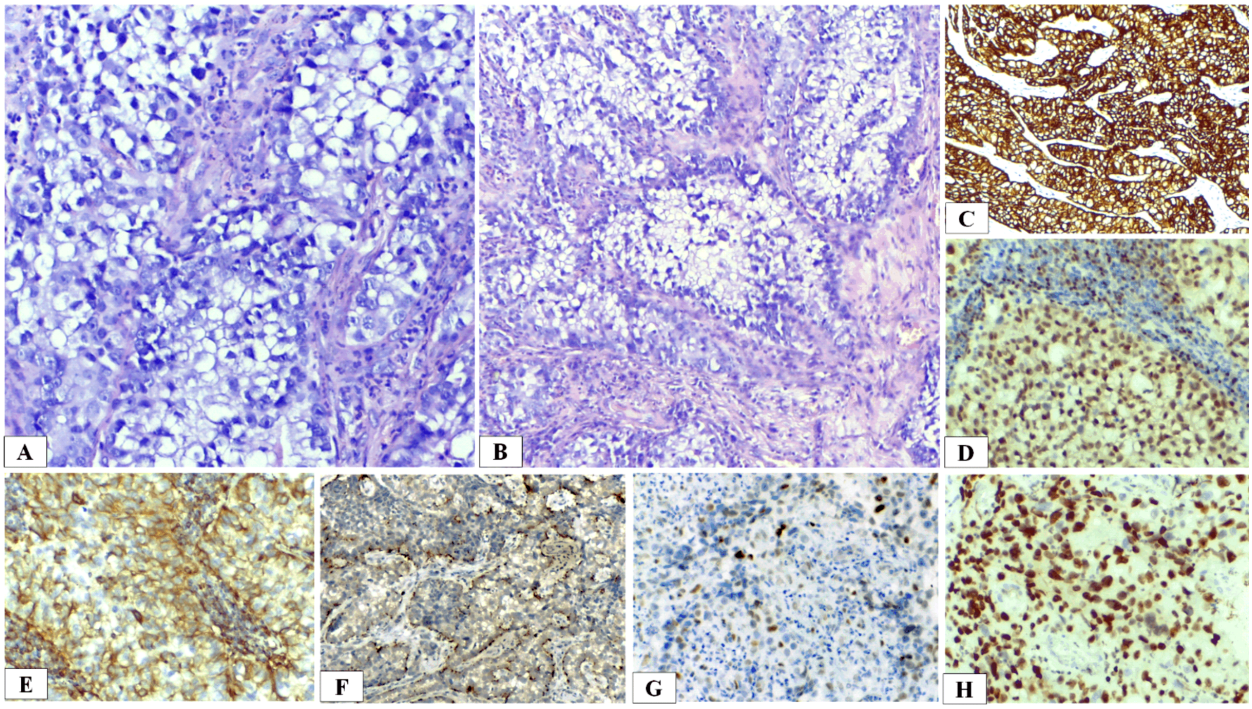

Figure 2 – ***(A and B) Clear cell carcinoma, solid pattern: diffuse sheets of clear tumor cells separated by thin fibrous septa [HE staining – ×200 (A), ×100 (B)]; (C) Diffuse reactivity for CK7 is present within the tumor (×40); (D) The malignant cells show widespread Pax8 expression (×100); (E) Focal vimentin staining is also present (×100); (F) Strong expression of napsin A in tumor cells (×40); (G) Moderate levels of p53 are detected in the tumor cells (×100); (H) About 70% of tumor cells express Ki67 (×100). HE: Hematoxylin–Eosin; CK7: Cytokeratin 7; Pax8: Paired-box 8.***

Discussions

CCCs could have developed from the Bartholin gland, but also could have originated in other organs of the female genital tract, adnexal glands of the skin, the kidneys, liver and lung, so a panel of antibodies were selected for narrowing down and exclude these possible tumor sites. Though unusual, genital cancers can metastasize in rare sites, like the spleen and also, other malignant tumors found in distant organs can metastasize in the genital organs, including the vulva [23, 24].

The restricted topography of CK7 makes it a good starting point for evaluating the origin of adenocarcinomas. This marker stains strongly positive in ovary, endometrium, cervix, breast, lung and pancreas carcinoma, but it is usually negative in yolk-sac tumors, hepatocellular carcinomas and renal tumors [25]. The biopsy was strongly and diffusely positive for CK7 (Figure 2C) thus providing with a few possible directions to investigate.

CEA is one of the most common antibodies used in IHC and it is positive in a large variety of adenocarcinomas: breast, lung, gastrointestinal tract, and pancreas, nevertheless it was proved to be negative in this specific case. CEA was used alongside ER, PR and p16 to differentiate between endometrial (ER+/PR+/CEA-/p16-) and endocervical (ER-/PR-/CEA+/p16+), but since all four antibodies were negative, all these possible sites were considered highly unlikely [26, 27]. Also, the US scan revealed a thin endometrium, with a thickness <5 mm, normal for postmenopause, that is extremely rarely associated with endometrial carcinoma [28].

Pax8 is highly expressed in endometrioid adenocarcinomas, uterine serous carcinomas, endometrial CCCs, non-mucinous and CCCs of the ovary [29]. The high specificity of this marker is particularly useful in distinguishing Müllerian (especially ovarian CCC) and renal carcinomas from metastases originating in the breast, lung, skin adnexa, adrenal glands [30]. The tumor was strongly and diffusely positive for Pax8 (Figure 2D), thus confirming our initial hypothesis that this tumor originates in the genital tract (Müllerian tract), or maybe less likely in the kidney, since the MRI exam revealed no tumor at this level.

The coexpression of vimentin (Figure 2E) and CK7 guides us to renal cell, endometrial, ovarian carcinoma [26].

Cutaneous metastases can occur in up to 11% of cases of renal CCC [31]. Because staining was negative for CD10, a specific marker for kidney tumors, it excludes a possible renal origin of the tumor, but the fact that CD10 is positive in the skin in sebaceous glands also eliminated this possibility [32]. Furthermore, p63 staining was negative, excluding other primary cutaneous neoplasm [31].

Most cases of CCC exhibit a distinctive morphological histological profile – glycogen rich clear cells, pattern that was also observed in our case. Nonetheless, in some cases, CCC can mimic other tumors, such as: serous borderline tumors, high grade carcinomas with serous or mixed serous/clear cells, other clear cell-rich neoplasms [33].

Recently, napsin A was introduced for confirming the diagnostic of CCC, with a high sensitivity of 82–100% in different studies [29, 33]. Also, this marker proved excellent specificity, staining positive in less than 1% of serous and 5–10% of endometrioid carcinoma cases [29, 33]. Moreover, the expression of napsin A is considered to have implications for the assessment of carcinomas of

unknown origin. A napsin A (+) and Pax8 (+) profile is considered specific for gynecologic tract adenocarcinomas and excludes a pulmonary origin [34]. In the case presented, napsin A was strongly and diffusely positive (Figure 2F) confirming the initial histological diagnostic of CCC.

Multiple studies have found that typical ovarian CCC correlates with p53-negative immunophenotype [35, 36]. The moderate p53 immunoreactivity (Figure 2G) and the absence of a primary ovarian tumor on MRI suggests that the vulvar tumor is very unlikely to be metastases of an elusive ovarian CCC. Calretinin was used to investigate a possible origin in sex cord stromal cells, but it was negative [27].

Ki67 is significantly higher in malignant tumors with poorly differentiated cells. It was also found that p53 expression is correlated with that of Ki67 [37]. The tumor had a high Ki67 index of 70% (Figure 2H) and also a moderate expression of p53 (30–40%) (Figure 2G) suggesting a poor prognosis regarding tumor progression, metastasis and survival. Despite the vulvar tumor's relative small size, the greatly enlarged inguinal, pelvic and para-aortic metastatic lymph nodes confirm the aggressive malignant behavior. Despite the effect of smoking on the concentration of different markers in pregnancy, it does not have any effect on neoplasm cell markers [38].

Current guidelines state that the standard treatment for early stage Bartholin gland carcinoma is primary surgery with radical exclusion with bilateral inguino-femoral lymph node dissection, followed by radiotherapy in case of positive margins or disease disseminated in the inguinal nodes [14, 39].

In first reported case of CCC of the Bartholin gland by Lim *et al.* [21], a 4–5 cm diameter partially cystic, partially solid tumor was described and no clinical signs of lymph node involvement. A wide local excision of the lesion was performed for diagnostic purpose followed by bilateral inguinal lymphadenectomy, when the diagnostic of CCC was established.

In the case reported by Chatzistamatiou *et al.* [22], the primary tumor localized at the level of the left Bartholin measured 2.2 cm in diameter with no signs of positive lymph nodes or secondary tumors. The patient underwent left hemivulvectomy and left inguinal lymph node dissection, because it was considered an early stage no adjuvant therapy was recommended.

Judging by the two reported cases in literature so far, there is no consensus regarding the treatment of Bartholin gland CCC. While both cases are stage I vulvar cancers, yet in one case hemivulvectomy and ipsilateral inguinal lymphadenectomy is performed and in the other only a wide local excision of the lesion, followed by bilateral inguinal lymphadenectomy.

The case presented in this article being an advanced stage – *International Federation of Gynecology and Obstetrics* (FIGO) – IVB, has a poor prognosis and limited therapeutic options. Currently, there is no standard approach to treat advanced vulvar carcinomas – FIGO stage III and IV. It is always important to tailor the therapeutic plan depending on the specific characteristics of the tumor since tumors involving the same organ can have very different responses to therapy depending on their histological and immunohistochemical profile [40].

Conclusions

Bartholin gland carcinoma is a pathology quite rarely encountered in practice. The positive diagnosis is eminently histological and IHC. Bartholin gland CCC is an extremely rare diagnosis with, to our knowledge, only two other cases reported in literature, but with a potential aggressive clinical behavior and poor outcome. Given the scarcity of Bartholin gland CCC cases reported in literature, there are no specific immunohistochemical markers described for this type of tumor.

Conflict of interests

The authors declare that they have no conflict of interests.

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