Abstract. Background: Malignant vaginal melanoma is extremely rare and accounts for fewer than 0.3% of all melanomas in women. Amelanotic malignant melanoma is a subtype of melanoma with little or no pigment on visual inspection. The simultaneous occurrence of amelanotic melanoma of the vagina and serous ovarian cancer is extremely rare. Case Report: A 61-year-old patient was referred to our hospital with recurrent ovarian cancer in association with a vaginorectal fistula. The first diagnosis was performed in 2009. The patient underwent multi-ovarian cancer recurrences after the primary cytoreductive surgery, especially in the vaginal vault, with several different lines of chemotherapy. The pathological results on this occasion demonstrated recurrent ovarian cancer with a component of amelanotic melanoma in the region of a vaginorectal fistula. Conclusion: We recommend detailed immunohistochemical staining, especially for recurrent ovarian cancer in combination with abnormal localizations or manifestations, in order to reveal any associations with another tumor.

Non-cutaneous melanoma is an uncommon form of melanoma. Malignant vaginal melanoma is extremely rare and accounts for fewer than 0.3% of all melanomas in women. This melanoma is a highly aggressive tumor, with an overall 5-year survival rate of 0-20% (1). Fewer than 150 cases of primary vaginal melanoma have been identified in a review of the literature (2). A small but important group of cutaneous melanomas can be classified as unusual variants. Amelanotic malignant melanoma is a subtype of melanoma with little or no pigment up-on visual inspection. It may mimic benign and malignant variants of both melanocytic and nonmelanocytic lesions. One large retrospective study reported that 50 (1.8%) out of 2881 patients with melanoma had an amelanotic primary or metastatic melanoma (3, 4). With cytodiagnosis, however, it is difficult to differentiate an amelanotic melanoma or a scantily pigmented melanoma from other conditions. It has been recently reported that immunohistochemical staining with HMB-45 is useful for the cytological and histological diagnosis of amelanotic melanoma (4, 5). The HMB-45 antibody stains a 10 kDa cytoplasmic glycoprotein thought to be part of the premelanosome complex (6). HMB-45 can be important in the evaluation of undifferentiated neoplastic lesions that are suspected of being melanomas.

Vaginal melanoma, although very rare, is a highly malignant disease. A literature review revealed only 21 reported cases with a survival of greater than five years. The most important factor for survival appears to be the tumor size. The treatment modality varied equally within the group of long-term survivors (27% radical surgery, 27% wide local excision, 27% radiotherapy, 14% wide local excision and radiotherapy, and 5% unknown therapy). The prognosis of patients with primary malignant melanoma is poor, regardless of the primary therapy (conservative or radical). The conservative treatment and the accurate investigation of every discolored lesion is recommended (7).

Improved clinical outcomes have been associated with surgical removal of gross disease areas whenever possible. Because of the low rate of lymph node metastasis, elective pelvic lymph node dissection is not obligatory. In cases of surgically unresectable disease, primary radiation therapy is indicated (1).
The majority of patients with epithelial ovarian cancer have an advanced-stage disease at the time of diagnosis. At least 60% of advanced ovarian cancer (stage III and IV) patients who achieve clinical complete-remission after complete primary therapy, will ultimately develop a recurrent tumor and will require further treatment (8). Despite advances in primary therapy of ovarian cancer, about two-thirds (67.5%) of the patients still suffer from a recurrence within the first five years. Since the disease in these women is no longer curable, the goal of therapy would be an improvement of the quality of life, a reduction of symptoms and when possible a prolongation of their life-span (9).

Secondary cytoreductive surgery can be considered for patients in whom disease recurs after a long disease-free interval (6 months or more) (10). The duration of such a disease-free interval has not yet been established, although most authors agreed that it should be at least 6 months before surgery is considered.

Metastatic involvement of the ovary from malignant melanoma is uncommon and presents a diagnostic challenge. Most cases are associated with disseminated disease and carry a dismal prognosis. Delayed ovarian recurrences from melanoma may mimic primary ovarian cancer and lead to aggressive cytoreductive procedures (11).

This article reports on a rare case of malignant amelanotic melanoma of the vagina with recurrent epithelial ovarian cancer.

Case Report

We report on a 61-year-old patient who was referred to Charité University Hospital with recurrent serous papillary ovarian cancer. The first diagnosis was performed in January 2009 (pT2a, L0, V0, N0, G3). Hysterectomy, bilateral adnexitomy, omentectomy, pelvic and para-aortic lymph node dissection had been performed. After the primary cytoreductive surgery, six cycles of chemotherapy with paclitaxel (175 mg/m²) and carboplatin (AUC 5) were given until June 2009. The patient underwent a complete tumor remission.

Figure 1. High grade serous carcinoma of the ovary with solid growth pattern, pleomorphic nuclei and high mitotic activity. A, Hematoxilin and eosin (original magnification ×300). B, MIB-1 (original magnification ×20). C, Immunohistochemical expression of CK7 (original magnification ×400).
Figure 2. Hematoxylin and eosin staining discloses crowded rounded or elongated cells within the distinct cytoplasm and hyperchromatic nuclei (original magnification, ×40).

Figure 3. Immunohistochemical study for HMB-45 (anti-melanoma protein mAb). The positive reaction (brown cytoplasmic reaction) supports the diagnosis of malignant melanoma (original magnification, ×400).
On January 25 2010, the patient was referred to our hospital again with an indication of secondary cytoreductive surgery, aiming at resection of an isolated tumor recurrence in the vaginal vault. After the second operation, a carboplatin-based regimen (AUC 5) with Caelyx (30 mg/m²) was given for six cycles, in terms of second-line chemotherapy. An early recurrence two months after the last cycle of second-line chemotherapy, again in the vaginal vault, indicated a third operation in order to eradicate the tumor from the vaginal cuff and to perform a systematic inguinal lymph node dissection.

At the end of 2010 another secondary cytoreductive surgery was performed to resect the residual of the omentum majus, with implementation of a partial colpectomy, and in order to obtain biopsies from the mesentery. This procedure was followed with six cycles of topotecan, 1.25 mg/m² weekly. The patient returned in August 2011 with recurrent disease in the vaginal cuff and in the splenic hilus. A vaginorectal fistula was diagnosed, and surgery, including the resection of tumor from the vaginal wall and splenectomy, as well as a protective double-barrel sigmoid colostomy, were performed. The pathological examination, this time, revealed recurrent ovarian cancer (Figure 1) with a component of amelanotic melanoma (Figure 2) in the region of a vaginorectal fistula. Immunohistochemical study for HMB-45 was deemed necessary to establish the diagnosis of amelanotic melanoma (Figure 3). The operation was performed without any complication, and the patient was discharged from the hospital 10 days later in a good condition.

Discussion

The simultaneous occurrence of amelanotic melanoma of the vagina and serous ovarian cancer is extremely rare. Pietzner et al. reported the case of a 35-year-old patient with ovarian manifestation of metastatic amelanotic melanoma and advised that clinicians should be aware of this differential diagnosis when treating ovarian cancer (12).

In our case, we report on a patient with recurrent ovarian cancer in the vaginal vault with a component of amelanotic melanoma arising from a vaginorectal fistula. The development of a tumor inside a longstanding fistula has already been reported in a few cases in the literature (13-16), but it is still an extremely infrequent event. Occasionally, the inflammation and the necrosis caused by the development and the progression of a tumor stimulates the formation of a fistula. However, there are instances in which the fistula is not a secondary manifestation of the neoplasia, and its formation predates the development of the tumor. In these cases, the neoplastic transformation arises inside the longstanding fistula, probably due to the latter’s chronic inflammatory nature (17). There are two published cases of melanoma presenting with fistulous formations, one concerning a biliary tract fistula (18) and the other presenting as a urethral fistula (19), in which the appearances of the fistulas were a consequence of the cancerous process.

Some reports claimed that malignant melanoma arising from a fistula harbored v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) gene mutations. The BRAF gene encodes a serine/threonine kinase involved in the mitogen-activated protein kinase pathway (MAPK) (20), and activating BRAF mutations are present in approximately 70% of cutaneous malignant melanomas (21) and in 82% of melanocytic naevi (22). More than 90% of BRAF mutations involve a single point mutation, T1799A, in codon 600 of exon 15, leading to a V600E amino acid substitution. However, several studies have shown that BRAF mutations are very uncommon in melanomas arising in sun-protected areas (23-25). These findings have suggested an association between the presence of BRAF mutations in malignant melanomas and ultraviolet (UV) light exposure. In some of the published articles, the role of BRAF gene mutations was emphasized in anal melanoma and in other parts of the body which are not associated with UV exposure, such as colorectal, ovarian and pancreatic cancer (26). The development of all of these tumor types may, in turn, also be related to inflammatory processes, in the same way as cutaneous melanoma is associated with inflammation of the skin caused by UV exposure. Accordingly, oxidative stress caused by inflammation may be in part responsible for mutations in the BRAF gene (24, 27).

A few studies have reported on BRAF gene mutations in ovarian cancer. The results of one study demonstrate that the mutational status of BRAF and V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) is distinctly different among various histological types of ovarian serous carcinoma, occurring most frequently in invasive micropapillary serous carcinoma, a clinically indolent neoplasm, and its precursors, borderline serous tumors. Thus, it appears that different histological types of ovarian carcinomas have distinct molecular pathways in tumor development (28).

About 50% of melanoma patients carry on their tumor, at least one, of the presently defined antigens, encoded by the melanoma antigen-encoding (MAGE), and the germanna antigen encoding (GAGE) genes (29). Currently, MAGE/GAGE genes have been identified and manipulated as tumor antigens in immunotherapy approaches for melanoma. Lei et al. reported that topotecan is capable of inhibiting the expression of MAGE mRNA of human peripheral blood (HPB-AM) cells in a time- and dose-dependent manner (30). This raises the question whether the emergence of melanoma in this case has any relationship with the chemotherapeutic agents that the patient received, especially topotecan (the last chemotherapy before the occurrence of melanoma). Similar approaches may be considered as an adjuvant therapy for
paclitaxel- or doxorubicin-treated breast or ovarian cancer patients who are likely to harbor subclinical occult disease. One study showed that melanoma cells from 37% of the patients contained at least one mutated MAGE gene (31). In our case, the vaginorectal fistula was not a longstanding one. It rose anew after the fourth operation and in a multi-operated region. Therefore we tend to suggest that this fistula was a result of the multi pre-operations in the same region, in combination with the emergence of recurrent serous epithelial cancer with a component of amelanotic melanoma, which may be evoked with a mutated MAGE gene induced by topotecan (or any other chemotherapy agents).

Conclusion

An amelanotic melanoma which is based on recurrent ovarian cancer is exceptionally rare, as is the presentation of melanomas with fistulous formations. We recommend that more detailed immunohistochemical staining should be performed (e.g. with HMB-45), especially for recurrent ovarian cancer in combination with abnormal localizations (isolated multiple recurrences in the vaginal vault), or abnormal manifestations (such as vaginorectal fistula), in orders to reveal any associations with other tumor components such as amelanotic melanoma. Clinicians should be aware of these rare conditions when treating ovarian cancer.

Conflict of Interest Statement

The Authors declare that there have no conflicts of interest.

References


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