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Primary malignant melanoma of the vagina: A case report

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ABSTRACT

Malignant primary melanoma of the vagina (PMV) is a rare type of non-cutaneous melanoma often discovered in postmenopausal women. PMV has a very aggressive disease course and a poor prognosis. The best course of treatment is not presently agreed upon. In this report, we describe the case of a 68-year-old woman presenting with a malignant PMV and its subsequent management. The patient presented with right vaginal pain, abnormal vaginal bleeding and a new vaginal mass. A PET scan identified a 28 × 38 mm hypermetabolic vaginal lesion, without nodal involvement or distant metastasis. A posterior exenteration type 2B was performed, including the anal mucosa. Sentinel lymph node dissection, vaginal and rectal resection as well as a terminal colostomy were also carried out. Final staging was FIGO stage III and T4bN1. Four months later, the patient presented with a recurrent vaginal bleed and intra-vaginal induration. Imaging revealed loco-reginal recurrence at the site of the primary malignancy with countless metastases. The patient opted for palliative care given the early disseminated recurrence and her multiple comorbidities. We review the treatment options for PMV, mainly the importance of surgery as the mainstay of treatment as well as the interest of adding checkpoint inhibitor immunotherapy or targeted therapy to the treatment plan. We also summarize the characteristics of PMV and its main prognostic factors.

1. Introduction

Malignant primary melanoma of the vagina (PMV) is an extremely rare type of non-cutaneous melanoma. It constitutes 0.2% of all melanomas (Jamaer, et al., 2020) and less than 3% of all malignant vaginal tumours (Rema et al., 2016). PMV possesses a very poor prognosis, mainly due to late diagnosis, poor visibility, early local recurrence, and high likelihood of distant metastasis (Kant, et al., 2018; Rapi, et al., 2017). PMV is most often discovered in postmenopausal women aged 60–80 years old (Jamaer, et al., 2020), who most commonly complain of vaginal bleeding, vaginal discharge or palpable vaginal mass within the distal third segment of the anterior vaginal wall (Chen et al., 2014). There is currently no consensus on optimal treatment. However, surgery, either local wide excision or more radical surgical interventions, remains the mainstay of treatment (Rapi, et al., 2017). Adjuvant treatments include radiotherapy, interferon-alpha immunotherapy, and chemotherapy, mainly with dacarbazine (Rapi, et al., 2017). While adjuvant checkpoint inhibitor immunotherapy is an established treatment option for patients with stage IIB/IIC and stage III cutaneous melanoma, data supporting this approach is limited for those with mucosal melanoma but is still often offered. For the uncommon patient with a BRAF V600 mutation-positive, targeted therapy would also be an option. The present study describes the case of a malignant PMV and its subsequent management.

2. Case report

We present the case of a 68-year-old woman presenting with malignant primary melanoma of the vaginal canal. The patient history is notable for a total hysterectomy and bilateral salpingo-ovariectomy for uterine fibroma, G3P2A0. Her other comorbidities include hypertension, diverticulitis, discal hernias, chronic fatigue, central vision loss and hepatic steatosis. The patient was also morbidly obese (Body Mass Index of 35.8) and needed a wheelchair to mobilize herself. The patient had an ECOG Performance Status Scale score of 3 and was thus only able of limited self-care and was confined to her chair or bed for more than 75%

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of her waking hours. The patient initially presented with right vaginal pain and abnormal vaginal bleeding for four months. The patient had also noticed a new vaginal mass two months ago and described two episodes of fecal incontinence. The patient also started having night sweats and noticed an exacerbation of her fatigue in the past 5 months to the point where they had to be lying down for 16 h each day.

Colposcopy revealed a 3 cm pediculated vaginal mass on the right wall of the distal third of the vagina, which included the anal mucosa and bled spontaneously. There were no palpable inguinal lymph nodes upon physical examination. The vaginal lesion was biopsied. The pathological report revealed a 1 mm malignant melanoma that did not show ulceration (Breslow II, T2aN0M0) and had 6 mitoses per high-power field (HPF). The tumor was extensively molecularly characterized. There was an absence of mutation in the KIT, EGFR, BRAF, KRAS, NRAS and PDGFRA genes. Immunohistochemical analysis revealed cancerous cells characterised as being positive for S100, MART-1 and Vimentine. The cancerous cells were negative for Myo D1, myogenine, caldesmone, CK AE1/AE3, CK7, CK20, CK5/6, p16, p40, PAX8, WT1, ER, PR, GATA3, EMA, desmine, SMA, p53. The cells were not reactive to the antibody directed against BRAFv600. Finally, the cancerous cells has an intact nuclear marking for BRG1, INI1, MLH1, MSH2, MSH6 and PMS2. An abdominopelvic CT scan, done in the context of a mild diverticulitis a month prior, had revealed no pelvic mass or lymphadenopathy. A subsequent PET scan identified a 28 × 38 mm hypermetabolic vaginal lesion, without nodal involvement or distant metastasis.

After discussion, the surgical team opted for a surgery with curative intent. A posterior exenteration type 2B, including the anal mucosa, was performed. During the operation, the same 3 × 4 cm budding lesion that had been previously discovered on physical exam was identified. It was situated on the right postero-lateral distal third portion of the vagina. Vaginal and rectal resection was achieved through an abdomino-perineal approach. A terminal colostomy was performed. The possibility of a colo-anal anastomosis had been evoked during previous conversations but was judged too precarious during surgery for a patient with severe mobility disorders since the distance to the anal sphincter was very short (less than 3 cm). Preoperatively, lymphoscintigraphy identified 3 sentinel lymph nodes, that were all on the right side; two right inguinal nodes and one right external iliac node. During surgery, a double technique was employed. Methylene bleu and technetium were used to identify these same lymph nodes that were then dissected perioperatively. Left ureterovesical reimplantation with concomitant ureteral stent placement was also performed because the ureter was accidentally completely sectioned perioperatively while trying to perform the removal of the invasive tumour. After the operation, the patient developed an ileus requiring parenteral nutrition for several days. She also required management of her high blood pressure and needed rehabilitation from the physiotherapy team given her deconditioned state. Thus, the patient was discharged 17 postoperatively.

At one month follow-up, the patient had a satisfactory evolution. The final pathological report indicated an 11.4 mm ulcerated malignant melanoma (Breslow stage IV, pT4b), with no lymphovascular invasion and clear surgical margins. There was no evidence of malignancy in the rectum or anus. The first right inguinal lymph node that was dissected was found to be positive without capsular extension. The second right inguinal lymph node as well as the right external iliac lymph node were negative. Nine colonic lymph nodes were examined and were also all found to be negative. Final staging was FIGO stage III and T4bN1. After discussion of the case with the Tumor Board and the patient, it was decided that no adjuvant chemotherapy or immunotherapy would be given due to her poor functional status.

Four months later, the patient presented with a recurrent vaginal bleed and intra-vaginal induration. Tranexamic acid was administered and a subsequent PET scan was scheduled. Imaging revealed locoreginal recurrence at the site of the primary malignancy with countless metastases within bilateral inguinal lymph nodes, both lungs, the liver parenchyma, the left proximal femur within the medullary cavity, and the left thigh within the subcutaneous tissues. Thus, the patient suffered an early disseminated recurrence. The patient opted for palliative care at home.

3. Discussion

The characteristics of the PMV reviewed here is consistent with what has been reported in the literature, i.e. a single localized melanotic lesion with high mitotic rate, often polypoid-ulcerated and bleeding easily with BRAF mutation almost always absent (Jamaer, et al., 2020; Rapi, et al., 2017). Several staging tools such as the FIGO and the TNM staging have historically been used for vulvar melanomas. However, the literature tends to favour the AJCC-TNM staging as the more pertinent one for prognosis (Rapi, et al., 2017).

The optimal treatment for malignant PMV has not yet been established. However, surgery is the primary treatment modality for curative intent (Jamaer, et al., 2020; Rapi, et al., 2017; Wohlmuth et al., 2020; Betschart, et al., 2007). In cases of early or local disease both conservative surgery (including wide local excision with adequate margins and partial vaginectomy) or radical surgery (such as pelvic exenteration, hysterectomy and total vaginectomy with pelvic lymph node dissection) seem to be the mainstay of treatment (Jamaer, et al., 2020; Chen et al., 2014; Rapi, et al., 2017; Wohlmuth et al., 2020; Betschart, et al., 2007). The choice of approach is controversial in the literature; Geisler advised primary pelvic exenteration for vaginal melanomas of more than 3 mm of invasion (Shih, et al., 2021); DeMatos stated that radical surgery would not improve survival rates compared to wide local resection but would improve quality of life (Frumovitz, et al., 2010) and Chen discussed that wide local excision was better utilized for unifocal disease whereas radical surgery was optimal for multifocal lesions (Chen, et al., 2014). Thus, there is no consensus on the optimal approach (Chen et al., 2014), but whichever surgical modality is deemed to best achieve complete resection of the disease, without unnecessarily opting for an exceedingly exhaustive intervention. In this case, we present a radical approach through the use of posterior pelvic exenteration and pelvic lymph node dissection.

Lymphadenectomy is not systematically performed due to the low rate of lymph node involvement (Jamaer, et al., 2020). Wohlmuth reported that, even among patients with sentinel node metastases, immediate complete lymph node dissection did not increase survival and was not necessary (Wohlmuth et al., 2020). However, lymph node status seems to be one of the most important prognostic factors for PMV (Jamaer, et al., 2020) and for this reason, assessing related nodes should be considered in all applicable patients (Wohlmuth et al., 2020; Geisler et al., 1995). Thus, within the case we present, despite absent lymphadenopathy on a CT scan or PET scan, surgical nodal staging was performed. In the literature, there are several reports of using pelvic radiotherapy as an adjuvant treatment after surgical resection (Chen et al., 2017; Tsvetkov, 2014). However, its efficacy remains controversial. Some authors discussed that radiotherapy did not have a significant impact on overall survival (Jamaer, et al., 2020) whereas other studies demonstrated a 13-month increase in survival as well as a decrease in risk of local recurrence when radiotherapy was used after local wide excision (14). Pelvic radiotherapy as a postoperative adjunct or even alone, in cases of unresectable tumours, has demonstrated improvements in prognosis within some studies (Chen et al., 2014). Furthermore, Kant et al. go on to conclude that surgery and post-operative radiotherapy is the mainstay of treatment (Geisler et al., 1995).

When the disease is advanced, disseminated, unresectable or recurrent, systemic treatments alone or in combination with radiotherapy for symptom control, are the recommended treatment modality (Jamaer, et al., 2020; Rapi, et al., 2017). Enrollment in a clinical trial, if available, is the preferred approach, but if not possible, initial treatment with programmed cell death 1 (PD-1) inhibitors alone or in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors is recommended rather than other systemic agents. While checkpoint

inhibition has less clinical efficacy in metastatic mucosal melanoma compared with metastatic cutaneous melanoma, it still offers the best chance for disease control and the possibility of extending survival (15). For patients with metastatic disease who are not eligible for immunotherapy such as those who progress on immunotherapy, have an intolerance, experience unacceptable toxicity to treatment or have comorbidities such as autoimmune disorders, targeted therapy for an actionable mutation, though rare, can offer a further line of therapy. At least, KIT, NTRK and BRAF mutations should be assessed and targeted if possible.

The 5-year overall survival of PMV is below 20% mainly due to late diagnosis related to poor visibility, early local recurrence, anatomical proximity to the vulvovaginal plexus, tumour biology, high likelihood of distant metastases and amelanotic tumours resulting in later diagnosis (Kant, et al., 2018; Rapi, et al., 2017). In the literature, mean recurrence-free survival is 16.4 months and mean overall survival is 22.2 months (Rapi, et al., 2017). In Frumovitz et al.'s study, disease recurrence was reported in 89% of patients and distant recurrence was reported in 88% of patients, mostly in the lungs and liver (14). Similarly, in our case, approximately 6 months after surgery, the patient presented with local–regional recurrence as well as countless disseminated metastases in bilateral inguinal lymph nodes, both lungs as well as the liver. Furthermore, even in cases of locally contained disease that underwent surgical intervention, local recurrence was between 30% and 40% (Jamaer, et al., 2020). The outcome of our patient might have been improved if her general condition had allowed adjuvant treatments to delay recurrence.

4. Conclusion

PMV is a rare gynecological cancer. It is mainly diagnosed in post-menopausal women presenting with abnormal vaginal bleeding, pain, or mass. PMV has an extremely poor prognosis due to its unique presentation, characterization, and evolution. There is currently no consensus for the optimal treatment of PMV. However, surgery remains the mainstays of treatment. In the metastatic and locally advanced unresectable setting, treatment is extrapolated from the approach used for metastatic cutaneous melanoma with lower responses rates but with the possibility of significant disease control, palliation and extending progression-free survival.

Author Contributions.

Giancarlo Sticca drafted the manuscript. Bojana Misheva conceptualized the project, collected the data, reviewed the article critically and made essential editorial changes to the manuscript. Vanessa Samouelian and Rahima Jamal reviewed the article critically and made essential editorial changes. Herawaty Sebajang was the supervisor, reviewed the article critically and made essential editorial changes. All authors approved the final version for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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