Long-term response of vulvar mucosal melanoma treated with neoadjuvant nivolumab

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INTRODUCTION

Mucosal melanoma is a particularly rare and aggressive subtype of melanoma. It represents only approximately 2% of all melanomas, and among them, 18% occur in female genital tracts (vulvar, vaginal, or cervical).[1,2] Prognosis for these patients is poor. The 5-year survival rate is 25%, much lower than that reported for cutaneous or uveal melanoma.[1] Complete resection of the primary tumor is the mainstay of treatment for resectable mucosal melanoma but is limited by surrounding structures due to anatomic location.[3] No guidelines currently exist for the treatment of vulvar melanoma specifically. Generally, radical vulvectomy is recommended for vulvar melanoma but requires aggressive surgical intervention associated with inherent significant morbidity, and local relapses can be observed.[4] There is no consensus review for the use of systemic therapy in mucosal melanoma.[5] A neoadjuvant approach with immune checkpoint inhibitors may facilitate surgery by reducing tumor size, but this procedure is not well studied with mucosal melanoma.[6] Here, we report the case of a long-term complete remission of a locally advanced vulvar melanoma treated with neoadjuvant nivolumab.

Abbreviation used:

PD-1: programmed death-1

CASE REPORT

A 59-year-old menopausal woman without children was referred by a gynecologist for a pigmented vulvar lesion. Physical examination revealed a pigmented ulcero-budding lesion on the labia minora, clitoris, and urethral meatus (Fig 1). The lesion was painful and associated with leucorrhea. The lymph nodes were free. Histological study of a cutaneous biopsy sample showed a mucosal lentiginous melanoma type, ulcerated, with a Clark level IV, a Breslow thickness of 4 mm, without regression, and a mitotic rate of 2/mm^2. The tumor was in the entire thickness of the biopsy sample. Immunohistochemistry was positive for melanin-A and PS100. No mutation was found in the 28-gene next generation sequencing panel analyzed, including *BRAF* mutation. No distant lymph node or visceral metastasis was observed with a brain and thoracic-abdominal-pelvis computed tomography scan. Pelvic magnetic resonance imaging showed a 3-cm vulvar mass invading the urethra. A complete tumor resection was proposed by total vulvectomy with urethral sacrifice and urinary bypass. This mutilating surgery was refused by the patient. Collaborative decision making led to a treatment plan of systemic treatment by neoadjuvant anti−programmed death-1 (anti−PD-1). The patient received her first monthly 480-mg nivolumab infusion in April 2020. Three months after initiating treatment, pain disappeared and physical examination showed partial regression of the tumor. After the third neoadjuvant nivolumab injection, a complementary surgery was proposed but was again refused by the patient. Anti−PD-1 therapy continued

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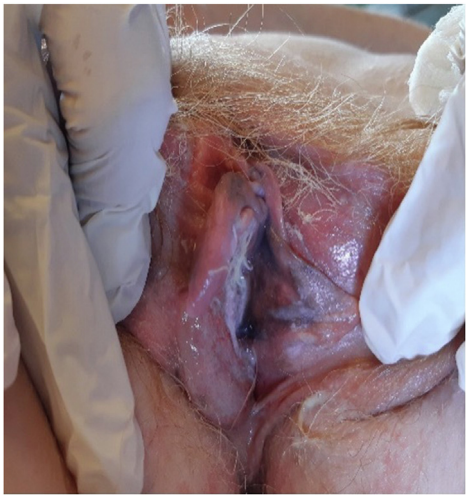

Fig 1. Vulvar melanoma invaded the labia minora, clitoris, and urethral meatus in April 2020.

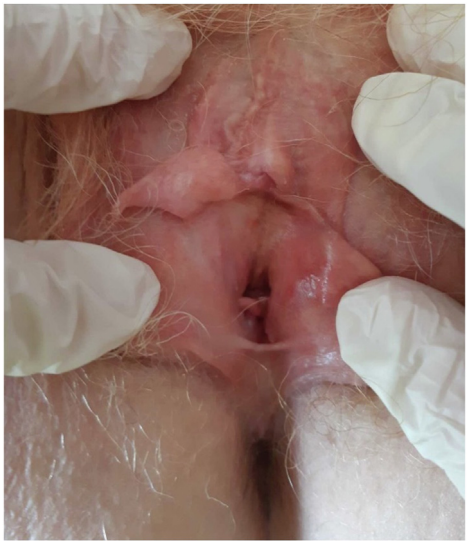

Fig 2. Complete response in April 2021, 12 months after treatment initiation.

as a curative treatment. After the sixth infusion, immune-related adrenal insufficiency was diagnosed. Evolution was favorable after hydrocortisone substitution. Twelve months after treatment initiation, clinical examination showed persistence of a little pigmented area of the labia minora (Fig 2). Skin biopsies did not find any residual tumor cells, and there was no hypermetabolism on positron emission tomography scan. Because of the complete response, no complementary surgery was proposed. The patient achieved nearly 2 years of a complete response, but nivolumab was discontinued after immune-related encephalitis. She is still in remission after 10 months of follow-up after anti—PD-1 discontinuation.

DISCUSSION

Mucosal melanoma is a rare and aggressive malignancy. Due to its rarity, mucosal melanoma is not reported separately in most clinical trials, and there are no well-established protocols for staging and treatment. Surgery is the treatment of choice for vulvar melanoma. Lesions should be treated with radical wide local excision, which often requires radical vulvectomy. Even with this aggressive surgical procedure, vulvar melanoma has poor prognosis with high recurrence rate.[7] Our patient refused this surgery because of the associated comorbidities, so systemic treatment was discussed. Neoadjuvant therapy is a promising therapeutic approach and has the advantage to quickly initiate a systemic treatment and to facilitate resection of the tumor in cutaneous melanoma.[8] Limited evidence exists to support the efficacy of immune checkpoint blockade with anti—PD-1 agents in the mucosal melanoma—specific subtype. A recent published retrospective study with 36 resectable mucosal melanomas treated with neoadjuvant checkpoint inhibitors (anti—PD-1 ± anti-CTLA4) demonstrated a signal of efficacy.[6]

Our case also suggests that nivolumab may be a therapeutic option for locally advanced vulvar melanoma and that neoadjuvant therapy can be an option, as in cutaneous melanoma. We chose nivolumab alone rather than a combination with ipilimumab because no study has reported statistically significant results for patients with mucosal melanoma who received a combination of or single checkpoint inhibitors at the time of treatment initiation.

To our knowledge, this is the first case reported in the literature of a vulvar melanoma treated with anti—PD-1 initially as a neoadjuvant therapy with a complete response since the 12th month of treatment that is maintained even after anti—PD-1 discontinuation for up to 10 months of follow-up.

Conflicts of interest

None disclosed.

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