Case Report

Vaginal Mucosal Melanoma: a Complete Remission after Immunotherapy and ‘0-7-21’ Radiotherapy Regimen (24 Gy/3 fractions/21 days)

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Abstract

We present the case of a patient with vaginal mucosal melanoma who underwent complete remission after immunotherapy and ‘0-7-21’ radiotherapy regimen (24 Gy/3 fractions/21 days). An 80-year-old woman had a biopsy of a voluminous vaginal lesion and received a histological diagnosis of melanoma with angiomatoid aspects. The patient underwent immunotherapy with pembrolizumab 2 mg/kg every 3 weeks and was sent to our attention for planning radiotherapy as the extent of the lesion did not make it susceptible to surgery. Considering the concomitant administration of pembrolizumab, we chose to treat this patient with a modulated intensity radiation therapy technique delivering a hypofractionated dose of 24 Gy in 3 fractions delivered on days 0, 7, and 21. We observed a complete clinical remission of the melanoma 12 months after radiotherapy and she has been alive for 18 months with no clinical signs of local recurrence.

Keywords
cancer, hypofractionation, immunotherapy, melanoma, radiotherapy

INTRODUCTION

Melanoma is a tumor that derives from melanocytes which are responsible for the production of the skin pigmentation. Although it is frequently a cutaneous neoplasia, in some cases it affects other districts such as the mucous membranes of the oral cavity and the urogenital system.1

In this regard, it is possible to find melanocytes in the basal portion of the vaginal epidermis of 3% of women2 and from these embryonic residues of the neural crest it is thought to derive the primitive vaginal melanoma which is a rare and aggressive tumor3 that can be unifocal or multifocal.4

The first case of malignant vaginal melanoma dates back to 1887, and a total of approximately 500 cases are included in the recent literature representing about 0.8% of female melanomas and <3% of all vaginal tumors.5 The age of incidence ranges from 40 to 90 years, whit a prevalence between 60-70 years.4 At diagnosis, 50% of patients have a lymph node invasion and 20% of patients have a distant...
metastatic disease due to the prevalent hematogenous spread of the tumor. To date, a standard therapeutic strategy for mucosal melanoma (MM) has not yet been established. Surgical approach includes both wide local excision (WLE) and radical surgery, and systemic therapies like chemotherapy and immunotherapy can be used alone or in combination. Radiotherapy (RT) is generally used with adjuvant purposes and in case of advanced or metastatic disease it represents only a palliative and symptomatic treatment. The radiation dose delivered in this kind of patients reflects the lack of uniformity due to the absence of clear guidelines in the therapy of MM as otherwise occurs in other clinical scenarios. Besides there are sparse data about the combination of immunotherapy and radiotherapy in the management of MM both in terms of radiation dose delivered and site of primary MM (i.e. head and neck, genitourinary, etc.).

The prognosis of melanoma is poor even in case of locally advanced lesions, in fact the 5-years overall survival is about 25% regardless of the therapeutic strategy adopted. Recent data suggest that anti/PD1 inhibitor therapies have activity against mucosal melanoma and Hamid et al reported the efficacy of Pembrolizumab in the treatment of locally advanced and metastatic mucosal melanoma in 84 patients included in KEYNOTE-001, 002 and 006 protocols. Here we report about a case treated with a combination of immunotherapy and irradiation using an unusual hypofractionated irradiation.

**CASE REPORT**

In February 2017 an 80-year-old woman had a biopsy of a voluminous vaginal lesion and received a histological diagnosis of melanoma with angiomatoid aspects. In the histological report it was described as a “poorly differentiated neoplastic proliferation with large deposits of intratumoral pigment; voluminous cellular elements with epithelioid morphology, arranged in aggregates including vascular structures, frequent mitotic figures and large deposits of intratumoral melanin pigment”, and its immunohistochemical profile was HMB-45+, Melan-A+, S100+, Ki-67 80%, BRAF wild type. The staging CT scan was negative for metastases, the lower abdominal MRI excluded the infiltration of adjacent organs such as bladder and rectum, and the $^{18}$F-FDG PET/CT revealed high vaginal metabolic activity with oncological negativity of the remaining body districts (Fig. 1). The patient started immunotherapy with Pembrolizumab 2 mg/kg every 3 weeks and was sent to our attention for planning RT as the extent of the lesion did not make it susceptible to surgery.

Considering the concomitant administration of pembrolizumab, we chose to treat this patient with intensity-modulated radiation therapy (IMRT) technique delivering a hypofractionated dose of 24 Gy in 3 fractions delivered on days 0, 7, and 21. We used the “verify Elekta” IGRT system followed by a treatment with Elekta Synergy®.

During the IMRT set-up our patient was placed on her back on the treatment table, and the Breast Board positioning system (Max3Plus, Bionic® Radiation Therapy) was used to reproduce the same gynecological position that the woman would have maintained during the treatment. The CT protocol (GE Optima CT660, United Kingdom) followed specific requirements for the XVI R4.2 system with 3.75 mm slice reconstruction, and the axial CT images thus obtained were transferred to the computerized treatment planning system (TPS) (Pinnacle3 treatment planning system, Philips) for the target volume and organs at risk (OARs) contouring; in particular, the gross tumor volume corresponded to the CTV and included both the tumor and the vagina. The IMRT treatment plan was obtained with an inverse planning algorithm, and it was verified using the Elekta XVI R4.2 system with M20 protocol (120 kV, 330 frames, 528 mAs, 22 mGy).

The dose to administer has been the most important matter of debate as long as data supporting a standard fractionated schedule rather than a hypofractionated one are still missing in the literature. Our patient underwent an extremely hypofractionated RT with a total dose delivered of 2400 cGy in 3 fractions administered at 0-7-21 days, and we decided to choose this schedule as it had provided promising results in the palliative treatment of a paranasal sinuses mucosal melanoma. The maximum dose (Dmax) delivered was 2460 cGy with a target coverage of 95% and a number of non-zero beams of 7. Regarding the OARs, the Dmax delivered was 750 cGy at the right femur, 840 cGy at the left femur, 2410 cGy at the bladder and 2390 cGy at the rectum, perfectly in line with the most recent data on tolerance of the OARs during extremely hypofractionated RT. A support therapy was prescribed at the beginning of the RT, and no acute (during irradiation) and late toxicities were recorded. As pembrolizumab toxicity hypothyroidism occurred and it was controlled with substitutive hormonal therapy.

At the end of treatment, at 21 days from the beginning, a 50% clinical remission of disease was obtained, then we re-evaluated the patient 12 months after RT and we observed a complete clinical remission of the melanoma (Fig. 2). In April 2018 patient had a progression of disease with liver metastases; at this time pembrolizumab administration was
suspended. In December 2018 she died without clinical sign of the primary vaginal melanoma.

DISCUSSION

In resectable vaginal melanoma the first approach is surgical as the complete removal of the macroscopic tumor has the best impact on the overall survival and the local disease control; the median survival in patients undergoing surgery is about 20 months.12–14 In early stage vaginal melanomas the WLE is recommended, but if for tumors with a Breslow depth <2 mm a safety margin of 1 cm is sufficient, for tumors with a Breslow depth >2 mm pelvic RT should be delivered.5,15,16 Patients with locally advanced disease usually undergo radical surgery and lymphadenectomy followed by chemotherapy and/or adjuvant RT2,17,18 whereas in patients not susceptible to surgery or which refuse it, the few data available in literature demonstrated a better local control of disease if RT is associated with chemo or immunotherapy.2,3 Up-to-date no standard fractionation exists, but using hypofractionated irradiation, additional biological effects resulting from endothelial cell damage, enhanced tumor immunity19–21 or both have been raised to account for the success of stereotactic techniques where dose of 8–30 Gy per fraction are delivered in one or more fractions.22 The patient of our case underwent RT with an IMRT technique in association with concomitant immunotherapy, but the novelty of this treatment was the choice of a 0–7–21 RT regimen with a “curative” intent. This kind of treatment schedule had been previously adopted exclusively with palliative purpose and without a concomitant systemic therapy.5,23 An hypothesis about the efficacy of this unconventional fractionation could be linked to the effect of high dose on tumoral cells which are in senescence or autophagic phase (reversible processes)24 during the interval between the first fraction (time 0), the second fraction (time 7), and the third fraction (time 21). Besides the concomitant use of immunotherapy could ameliorate the immunogenic effect of high dose such as 8 Gy delivered 3 times in 21 days. This hypothesis is conjectural and should be confirmed in radiobiological studies. We believe that ours is a feasible therapeutic approach that can be proposed to elderly patients unfit for surgery or which refuse it. With this treatment, in fact, a complete clinical local remission of disease was obtained at 12 months, showing how our approach can have an impact on the local disease control. Finally, a high tolerance to the treatment has been demonstrated by the absence of acute toxicities and loco-regional chronic sequelae and by the preservation of the anatomical functionality.22,23,25

Conflict of interest

The authors declare neither conflict of interest nor financial disclosure.

Authors’ contributions

S.Par, S.L., and A.C.: conception and organization of the work, literature research and interpretation, writing of the first draft and revision of the final version of the manuscript.
A.S., C.P., A.P., N.S., T.F., and C.T: literature research and interpretation.
S.Perg.: conception and organization of the work, literature research and interpretation, critically revised the manuscript, and guarantor and supervisor of the research project.

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Меланома слизистых оболочек влагалища: полная ремиссия после иммунотерапии и режима лучевой терапии «0-7-21» (24 Gy / 3 фракции / 21 день)

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Резюме

Мы представляем случай больной с меланомой слизистых оболочек влагалища, которая вышла в полную ремиссию после курса иммунотерапии и лучевой терапии «0-7-21» (24 Gy / 3 фракции / 21 день). 80-летней женщине была выполнена биопсия объёмного влагалищного образования и была гистологически диагностирована меланома с ангиоматоидными аспектами. Пациентка прошла курс иммунотерапии пембролизумабом в дозе 2 мг / кг раз в 3 недели и была направлена к нам для планирования лучевой терапии, поскольку распространение образования не делало его доступным для хирургического вмешательства.

Учитывая сопутствующее применение пембролизумаба, мы решили лечить пациента методом радиотерапии с модуляцией интенсивности, обеспечивающим гипофракционированную дозу в 24 Gy 3 фракций, вводимых в дни 0,7 и 21. Мы наблюдали клиническую ремиссию меланомы через 12 месяцев после лучевой терапии, и пациентка жива через 18 месяцев после лечения без клинических признаков местного рецидива.

Ключевые слова
рак, гипофракция, иммунотерапия, меланома, лучевая терапия