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CLINICAL VIGNETTE

Management of Vaginal Mucosal Melanoma

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Case

An 80-year old woman with diabetes, hypertension and coronary disease developed vaginal bleeding. Her gynecologist found a pigmented polypoid mass involving the lower anterior vaginal wall with pigmented lesions in cervix, vaginal fornix, and bilateral vulvar areas, without inguinal adenopathy. Biopsies of vaginal and cervical lesions showed malignant melanoma. Because of locally advanced presentation, staging studies were obtained, including normal MRI brain and pelvis as well as PET CT scan showing no adenopathy and no evidence of distant metastasis.

She underwent surgical debulking of the vaginal mass and pathology confirmed multifocal malignant melanoma. Molecular profile showed the presence of KIT mutation at exon 11 (p.F584_P585Ins LYDHWKWEF) and BRAF wild type status. After recovery from surgery, she started systemic immunotherapy with nivolumab every two weeks. Four months after starting immunotherapy, she developed recurrent vaginal bleeding and another vaginal mass. Repeat PET CT show no distant metastasis and she underwent a second debulking surgery. Surgical pathology showed recurrent malignant melanoma. She completed adjuvant radiation with continuation of nivolumab. Three months later, surveillance PET CT showed new lung and liver metastasis. The patient entered a clinical trial and started second line immunotherapy but developed central nervous system metastasis. She completed whole brain radiation therapy and started third line ipilimumab. Repeat imaging showed further disease progression and she was transitioned into hospice.

Introduction

Primary vaginal mucosal melanoma is a very rare malignancy of the female reproductive tract. Vaginal melanoma constitutes 0.3% to 0.8% of all melanomas in women and fewer than 3% of malignant vaginal tumors.¹ It is often seen in women in the 6th or 7th decade of life. Common presenting symptoms are similar to other gynecologic malignancies. These include vaginal bleeding, abnormal discharge, pruritus, burning pain, dysuria, and the presence of a mass or ulceration. Most vaginal lesions are pigmented but some can be amelanotic.² Vaginal melanomas most commonly originate from the lower third of the anterior vaginal wall.³

Vaginal melanomas arise from malignant transformation of melanocytes, which are present in small numbers in mucous

membranes. Unlike cutaneous melanoma which are related to exposure to ultraviolet light, no distinct environmental risk factors have been associated with vaginal melanoma. Family history of cutaneous melanoma may increase risk of vaginal melanoma. The diagnosis of vaginal melanoma is usually established by biopsy of suspicious mucosal lesion or mass. The most common growth pattern is nodular for vaginal melanomas.⁴ Histologically, approximately 55% are of the epithelioid subtype, 17% spindle cell and 28% mixed type.⁵ The pathologic diagnosis of melanoma is established by immunohistochemistry (IHC) pattern showing positivity for S-100, melan A, HMB-45, and vimentin. IHC results are typically negative for cytokeratin, chromogranin, and negative for estrogen and progesterone receptor expression.

Clinical staging of vaginal melanoma (VM) follows the International Federation of Gynecology and Obstetrics (FIGO), while pathological staging is based on the American Joint Committee on Cancer (AJCC) TNM staging method. In general, FIGO stage I is tumor confined to vagina. Stage II has clinical evidence of tumor invading paravaginal tissues but not pelvic wall. FIGO stage III reflects pelvic or inguinal lymph node involvement, or tumor extension to pelvic wall. FIGO stage IV is subdivided into IVA and IVB: IVA is tumor invading bladder or rectal mucosa, or tumor extension beyond true pelvis. IVB disease has distant metastasis. VM has an aggressive clinical course with relatively short median survival rates. Data from the Surveillance, Epidemiology, and End Result (SEER) registry demonstrated median survivals of 22, 9, 23, and 6 months respectively for FIGO stages I, II, III, and IV.⁶ This same registry showed 2- and 5-year overall survival rates of 23.5% and 15.4%. The 3-year overall survival rate for patients with lymph node positive disease was 6.6% versus 31.9% for lymph node negative status.

Localized vaginal melanomas amenable to surgical resection, undergo wide local excision (WLE) with establishment of adequate tumor-free circumferential margins. This offers the best chance of prolonged disease-free survival. More radical surgical resections have failed to show an improvement in loco-regional control or survival when compared to WLE.⁷ Patients with resectable VM with inguino-femoral adenopathy should discuss benefit of lymphadenectomy balanced by long-term risk of lower extremity lymphedema. Therapeutic options are more restricted for patient with VM who present with locally advanced disease. There are no studies supporting preoperative

systemic therapy to downstage VM into resectable disease. Furthermore, definitive treatment with radiation therapy has been inferior when compared to combined modality treatment with surgery plus radiation. This may be due to inherent radio-resistance of mucosal melanomas. Therefore in highly selected patients with locally advanced VM, surgical cytoreduction can be considered, followed by a course of adjuvant radiation therapy.

A novel approach incorporates immunotherapy with the checkpoint inhibitor ipilimumab. This was retrospectively studied in three patients with VM at Memorial Sloan Kettering Cancer Center.⁸ All three received treatment with ipilimumab with either concurrent or sequential external beam radiation therapy (EBRT) followed by surgical resection. Of the two surviving patients completing immuno-radiation therapy (IRT), one had stable disease and second one had a complete response. Both patients were in complete response by imaging after surgery. Both were alive with no evidence of disease at 20 and 38 months of follow up.

There is no established standard of care for systemic treatment of patients with advanced metastatic FIGO stage IVB vaginal melanoma. Overall response rates to standard cytotoxic chemotherapy are low and of short duration. Therapy is often extrapolated from newer non-chemotherapy based treatments commonly used to treat advanced metastatic cutaneous melanoma. Molecular profiling of cutaneous melanoma identified somatic mutations enabling use of targeted therapy with substantial clinical benefit. Approximately 62% of cutaneous melanomas are positive for activating V600E or V600K mutations in BRAF gene.⁴ Molecular profiling in patients with vaginal melanoma has potential therapeutic implications. Comprehensive molecular analysis was performed in 51 patients with vulvar and vaginal melanomas, including 14 patients with vaginal melanoma. In the combined group, a BRAF mutation was identified in 26% of cases and a KIT mutation was noted in 22%.⁹ Interestingly, KIT mutations were more common in vulvar (9 of 34 tumors) versus vaginal melanomas (1 of 12 tumors). PD1 and PDL1 expression were 75% and 56% respectively. Of the distinct BRAF variants detected, six had V600E activating mutation, associated with increased sensitivity to BRAF inhibitors. On the other hand, 40% harbored a KIT mutation variant with a leucine-to-proline substitution at codon 576 (L576P), reported to be an actionable target for various KIT inhibitors such as imatinib.

Combined oral therapy with BRAF inhibitor plus MEK inhibitor is a current standard of care for patients with advanced metastatic cutaneous melanoma with an activating BRAF mutation. Single agent vemurafenib has demonstrated activity in advanced mucosal melanoma. In a small cohort of 10 patients with BRAF V600E mutation, overall response rate was 40% with disease control in 9 out of 10 patients and median survival of 11.7 months.¹⁰ Although tumor response and clinical benefit in cutaneous melanoma is significant with BRAF inhibitor monotherapy, acquired resistance invariably develops.¹¹ One mechanism of acquired resistance involves development of

mutations in MEK gene, which bypass BRAF inhibition and allow cell proliferation and survival culminating in melanoma progression.¹² Combined therapy with BRAF inhibitor plus MEK inhibitor has successfully overcome this type of acquired resistance in cutaneous melanoma. Unfortunately, there are no published reports on efficacy and safety of combination therapy for advanced metastatic mucosal melanomas harboring a BRAF mutation. Participation in clinical trials is recommended. ECOG-EA6134 involves sequential treatment with immunotherapy and dabrafenib-trametinib combination as first line treatment of advanced cutaneous melanoma harboring BRAF V600 mutation.¹³ This clinical trial also includes patients with primary mucosal melanomas.

An alternative targeted therapeutic option for advanced mucosal melanomas is imatinib. Imatinib has been successfully used to treat other solid malignancies with overexpression of c-KIT oncogene such as gastrointestinal stromal tumors. The c-KIT gene encodes the stem cell factor (SCF) receptor which when bound by SCF ligand results in activation of downstream signal transduction pathways.¹⁴ In cutaneous melanoma, this ligand-receptor interaction results in proliferation, migration, and survival of malignant melanocytes. Both cutaneous and mucosal melanomas are associated with various degrees of KIT overexpression. Satzger and colleagues reported 40 out of 44 (91%) of mucosal melanoma tumor specimens had at least 10% KIT staining by immunohistochemistry (IHC).¹⁵ Nonetheless c-KIT overexpression by IHC has not proven to be a reliable biomarker predicting clinically meaningful responses to treatment with imatinib. Further molecular studies identified hotspot mutations within c-KIT gene which have been better predictors of therapeutic response to imatinib. Most KIT mutations in melanoma are substitutions of a single amino acid in exons 11, 13, and 17 which affect the juxtamembrane domain of KIT protein, and lead to constitutive activation of KIT independent of ligand binding. The clinical benefit of imatinib in the treatment of advanced mucosal melanoma has been described in a small number of trials. A Phase II study by Hodi et al, reported 13 out of 24 patients harboring a KIT mutation, with response rates imatinib compared to those with KIT amplification only.¹⁶ Best overall responses were noted only in patients harboring KIT mutations, not in those with only KIT amplification. Interestingly there were no significant differences in response based on melanoma clinical subtype, although most responses, 41%, were noted in mucosal melanomas. Similar modest clinical benefit was demonstrated in Phase II trial by Guo et al in which patients with advanced cutaneous and mucosal melanoma received treatment with imatinib.¹⁷ In this study the median PFS (progression-free survival) was 4 months in patient with KIT mutations in exons 11 or 13 versus 2.2 months in patients with other KIT aberrations.

Immuno-oncologic therapies have shifted the therapeutic paradigm for Hematologic and Oncologic malignancies. Checkpoint inhibitors are now the standard of care for patients with advanced cutaneous melanoma, due to significant improvements in survival rates. Checkpoint inhibitors have also demonstrated clinical efficacy in advanced mucosal

melanoma. In this context, the data is much more limited and based largely on retrospective series or subset analyses of prospective trials. Shoushtari et al published a multi-institutional retrospective cohort analysis assessing activity of single agent nivolumab or pembrolizumab.¹⁸ This study identified 35 patients with advanced mucosal melanoma who received treatment with either checkpoint inhibitor. The overall response rate for this subtype of melanoma was 23%, with a median follow up of 10.6 months and median PFS of 3.9 months. At the time of publication, data was not mature enough to report median overall survival (OS). There is also a paucity of data regarding the therapeutic combination of nivolumab plus ipilimumab in advanced metastatic mucosal melanoma. D'Angelo et al conducted a pooled analysis across multiple clinical trials assessing efficacy and safety of nivolumab monotherapy versus combination treatment with ipilimumab in a subset of patients with advanced mucosal melanoma.¹⁹ In this pooled analysis, 86 patients were identified with mucosal melanoma, and 35 received treatment with combination nivolumab plus ipilimumab. They reported median PFS with combination therapy of 5.9 months. There was significant improvement in PFS in a selected population with tumor PD-L1 expression of 5 or more percent, where the PFS had not been reached. A similar beneficial effect of tumor PD-L1 expression was noted in overall response rate. The response rate in the unselected population was 37% versus 60% with tumor PD-L1 expression of 5 or more percent.

Conclusion

Primary vaginal mucosal melanoma is a very rare malignancy, accounting for less than 1 percent of all melanomas. Because of its rarity, distinct biology, clinical presentation, and anatomical location, the optimal treatment strategy remains undefined. Complete wide local excision remains the standard initial treatment for resectable disease. Despite surgical intervention, many patients will experience recurrence with distant metastasis. Treatment of metastatic vaginal mucosal melanoma is largely extrapolated from experiences in treating advanced cutaneous melanoma with checkpoint inhibitors and oral therapies targeting driver oncogenic mutations. Unfortunately, outcomes continue to be suboptimal with available therapies so clinicians should continue to encourage active participation in well-designed prospective clinical trials.

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