

Case Report

Primary gynecologic melanoma: A report of two unusual cases

Jessica L. Berger^{a,*}, Daman Samrao^b, Marilyn Huang^a, Alexander B. Olawaiye^a^a Division of Gynecologic Oncology at Magee-Women's Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, United States^b Department of Pathology at Magee-Women's Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, United States

ARTICLE INFO

Article history:

Received 24 October 2014

Accepted 11 January 2015

Available online 17 January 2015

Keywords:

Cervical melanoma

Ovarian melanoma

Immunotherapy

Multidisciplinary treatment

ABSTRACT

Background: Primary ovarian and cervical melanomas are extremely rare tumors with a poor prognosis. Diagnosis requires a high index of suspicion as presentation can mimic benign conditions clinically and other neoplasms histologically.

Cases: A 41 year-old with an adnexal mass underwent surgical staging for a stage IA ovarian melanoma. Imaging revealed a brain metastasis treated with radiation. Subsequent nodal recurrence was treated with immune and targeted therapies. She is alive with disease at 61 months follow-up. A 54 year-old presented after endocervical melanoma was diagnosed with polypectomy. She underwent radical hysterectomy, lymphadenectomy, and adjuvant brachytherapy. Immediate post-treatment imaging revealed widespread liver and pulmonary metastasis, currently being treated with ipilimumab.

Conclusion: Immunohistochemistry can facilitate the diagnosis of gynecologic melanoma, and multidisciplinary treatment is recommended.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Rates of malignant melanoma have increased dramatically over the last 20 years with 76,100 new diagnoses expected in 2014 (Siegel et al., 2014). Of these, genital tract melanomas make up 0.23% of all melanoma cases and 18% of mucosal melanomas (Sugiyama et al., 2008). The majority of melanoma arising in the genital tract is vulvovaginal in origin. Other gynecologic sites are extremely rare with approximately 81 primary cervical melanoma cases and 42 primary ovarian melanoma cases reported in the literature, the majority of the latter are found in association with ovarian teratomas (Sugiyama et al., 2008). Presentation of these rare malignancies can be similar to benign neoplastic processes, and pathologic assessment can be complicated by the heterogeneous appearance of these tumors. Here, we report two rare cases of gynecologic melanomas: primary ovarian melanoma, alive with disease at 62 months follow-up, and stage IB1 endocervical melanoma with rapid disease progression.

Cases

Case 1: A 41 year old presented with an abdominopelvic mass, cystic with septations and measuring 16 × 17 × 12 cm on axial imaging. Surgical evaluation was recommended and intraoperative

frozen section revealed a poorly-differentiated epithelial neoplasm. Complete surgical staging was performed with hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, omentectomy, and appendectomy. Her post-operative recovery was uncomplicated. Final histopathology revealed a stage IA ovarian melanoma. Immunostains for S100, HMB-45, and Mart-1 were positive (see Fig. 1). Interestingly, there was not an associated teratoma, and a thorough skin survey failed to reveal another primary lesion.

Metastatic evaluation 2 months after diagnosis revealed a 1.2 cm brain metastasis, but no other diseases. She underwent stereotactic radiosurgery and adjuvant high-dose alpha 2B interferon. Seven months after completion of primary therapy and 25 months after diagnosis, she recurred in the paraaortic lymph nodes and had a partial response with high-dose interleukin-2 and aflibercept, which was durable on maintenance aflibercept. She underwent surgical resection for residual paraaortic disease, and pathologic evaluation identified a BRAF mutation. Subsequent therapy included the targeted agent vemurafenib, which she progressed on after 8 months of therapy, followed by a partial response to ipilimumab, which was durable for 14 months. She is currently on pembrolizumab 69 months after diagnosis.

Case 2: A 54 year old post-menopausal female was referred following the removal of a 4 cm endocervical polyp with final histopathology demonstrating a malignant melanoma with positive margins. Immunostains for S100, HMB-45, and Mart-1 were positive (See Fig. 2). A staging PET/CT scan was negative for metastatic disease, and a pelvic MRI demonstrated a 23 × 22 × 49 mm cervical lesion with concern for parametrial extension. The patient underwent a type-III radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy with residual

* Corresponding author at: Division of Gynecologic Oncology, Magee-Women's Hospital of the University of Pittsburgh Medical Center, 300 Halket Street, Suite 2130 Pittsburgh, PA 15213, United States. Fax: +1 412 641 5417.

E-mail address: bergerjl@upmc.edu (J.L. Berger).

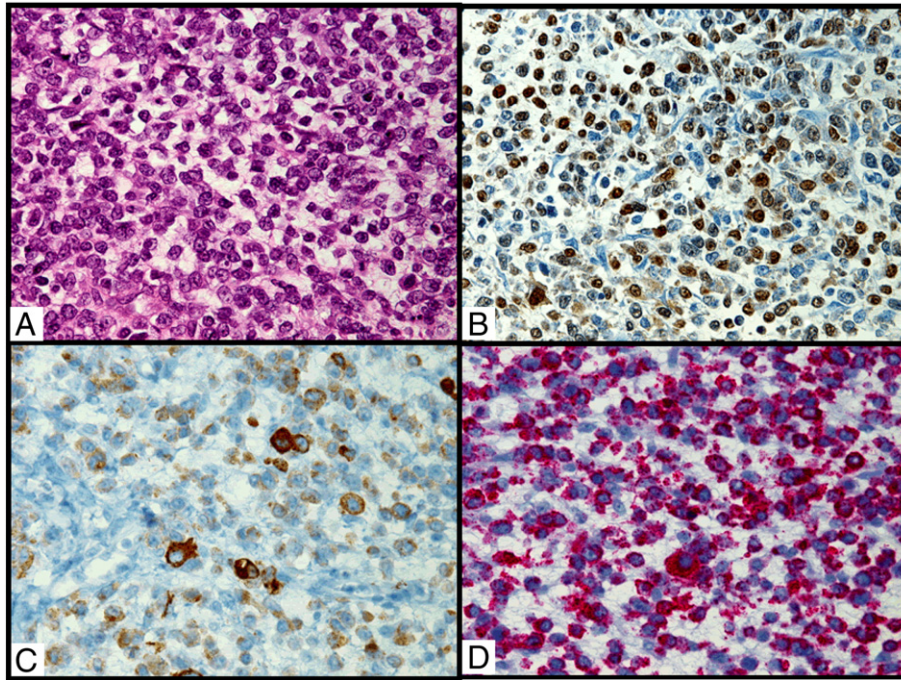


Fig. 1. (A) High power (40 \times) H&E of primary ovarian melanoma. Positive melanoma immunostains; (B) S100, (C) Mart 1 and (D) HMB45.

amelanocytic melanoma involving the full thickness of the cervix and extending to the vagina with extensive angiolymphatic invasion. All margins were negative, as were 26 pelvic lymph nodes. Her post operative course was complicated by a small bowel obstruction that resolved with conservative management as well as a pelvic abscess which required percutaneous drainage and antibiotics. A multidisciplinary team recommended high-dose rate brachytherapy given the high-risk features, which was completed 8 weeks after surgery, followed by systemic therapy with ipilimumab. Unfortunately, she was hospitalized for nausea and vomiting post-radiation, and imaging revealed metastatic

disease with innumerable new liver and pulmonary metastases that were not present on imaging 6 weeks earlier. She was lost to follow-up and died of disease 2 months later (7 months from initial diagnosis) without receiving systemic therapy.

Comment

Gynecologic melanomas are rare malignancies which can be difficult to diagnose and have a significantly worse prognosis than cutaneous melanoma, with 5 year survival rates of 11–25% compared to 81%

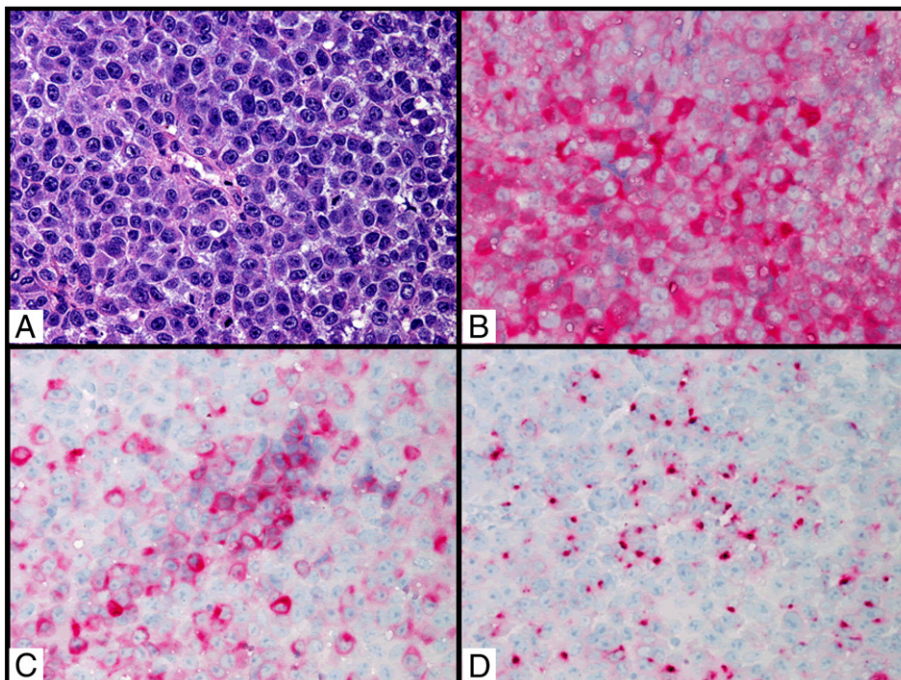


Fig. 2. (A) High power (40 \times) H&E of primary cervical melanoma. Positive melanoma immunostains; (B) S100, (C) Mart 1 and (D) HMB45.

(Sugiyama et al., 2008; Carvajal et al., 2012). Gynecologic melanomas can have a variety of morphologic appearances, creating a wide differential diagnosis when not suspected clinically, and immunohistochemistry can be helpful in establishing the diagnosis (Carvajal et al., 2012). Melanoma will frequently stain positive for S100, vimentin, Mart 1, and HMB45. The combination of S100, which is more sensitive, and HMB45, which is more specific, provides the most accurate diagnostic criteria (Deshpande and Munshi, 2001). There are no known risk factors for the development of gynecologic melanomas and universal staging systems have not been shown to be predictive of clinical outcome. The International Federation of Gynecologic Oncology staging system has been shown to correlate with survival in cervical melanomas and the Clark and Breslow systems have been proposed to have better prognostic estimates for dermoid-associated ovarian melanoma (Sugiyama et al., 2008; Carvajal et al., 2012). Prognostic factors are site specific and not well-defined for rare sites (Carvajal et al., 2012).

Surgical resection with wide margins remains the standard treatment of melanoma, but can be challenging due to the multifocal nature and lentiginous growth pattern of mucosal melanoma, as well as anatomic constraints of the primary site (Carvajal et al., 2012). Many patients will recur distantly regardless of margin status, so morbidity of initial resection must be balanced with overall prognosis. Because of the high rate of local recurrence, post-operative radiotherapy has become widely used in mucosal melanoma of the head and neck, with improved local control rates in several series (Carvajal et al., 2012). This benefit has not been confirmed in prospective clinical trials and has not been demonstrated to impact overall survival, likely due to the high rate of distant metastasis. Systemic therapy has not been specifically evaluated in mucosal or gynecologic melanomas and has generally mirrored that of cutaneous melanoma, including immune therapies such as interleukin-2 and ipilimumab, as well as targeted therapies, and to a lesser extent, cytotoxic chemotherapy (Carvajal et al., 2012).

There have been 42 cases of primary ovarian melanoma reported in the literature since 1901. The ovary does not contain melanocytes, and most reported cases identified a coexistent teratoma as the purported origin of melanocytes in the ovary. Proposed diagnostic criteria for primary melanoma of the ovary includes association with a teratoma in addition to exclusion of another primary site (Cronje and Woodruff, 1981). The current case did not have teratoma elements identified on histopathology, and thorough evaluation did not reveal another lesion at presentation. It is possible that this was metastatic cutaneous disease with regression of the primary lesion, however, the pattern of subsequent relapse in the paraaortic nodal chain is consistent with an ovarian primary. Presumably, this case arose from a small dermoid cyst or monodermal teratoma that was then obliterated by bulky tumor growth.

The prognosis following an ovarian melanoma has been dismal, even with disease confined to the ovary. Only one patient reported in the literature has lived longer than 30 months and was without evidence of disease at 5 years follow-up (Carlson and Wheeler, 1993). The current case of ovarian melanoma represents the longest survival reported, 69 months, despite metastatic disease early in her disease course. It is also the second report of ovarian melanoma treated with immunotherapy suggesting a role for biologic agents and multimodal therapy. The remainder of reported patients were treated primarily with surgery, less than half receiving adjuvant chemotherapy.

Eighty-one cases of primary cervical melanoma have been reported in the literature. Cervical mucosal melanoma usually presents as vaginal bleeding or vaginal discharge. The basis of treatment is surgical excision with wide margins, though there is no consensus on the optimal surgical approach to this disease; radical hysterectomy with pelvic

lymphadenectomy is frequently employed. Radiation has generally been used for patients with advanced or unresectable disease, positive margins or lymph nodes, parametrial involvement, or palliative treatment of recurrence (Myriokefalitaki et al., 2013). Adjuvant radiation has been successful in local control of head and neck mucosal melanomas, and may be applicable to other mucosal sites with high-risk features. There are no cytotoxic chemotherapeutic regimens which have proven effective in the treatment of mucosal melanoma. Recent success in the treatment of cutaneous melanoma with immune modulating and targeted therapies have not been specifically evaluated in mucosal melanoma and have not been previously reported in cervical melanoma (Mousavi et al., 2006). Prognosis, regardless of stage at diagnosis or treatment approach, is poor. Five-year survival rates for stage I disease range from 18.8–25%, 11.1–14% for stage II disease, and 0% for stage III and stage IV disease (Sugiyama et al., 2008; Myriokefalitaki et al., 2013). Rapid disease recurrence or progression can occur locally or distantly early after diagnosis, as was seen in this case. Early visceral metastasis has universally been emphasized as an extremely poor prognostic factor (Mousavi et al., 2006).

The strongest prognostic features of both disease sites are negative resection margins and stage at diagnosis. Despite complete resection of local disease, both cases had early distant metastasis. The fulminant disease course of the cervical melanoma case compared to the ovarian melanoma, may reflect the difference in biologic behavior of mucosal versus cutaneous melanoma. The disparate outcomes of these two cases highlight the limitations of traditional prognostic features, and future study into molecular mechanisms of tumor biology may provide more accurate clinical predictors.

In summary, we present two cases of rare gynecologic melanoma treated with multimodal therapy by an interdisciplinary team. Ovarian and cervical melanomas require a high index of suspicion from both the treating gynecologist as well as the pathologist. Immunohistochemistry can be instrumental in making the diagnosis. Prognosis is particularly poor and optimal treatment is not known due to the rarity of these malignancies, but generally mirrors that of cutaneous melanoma. The basis of treatment is surgical excision with wide margins and should include a subspecialist familiar with radical surgery at the primary site of the tumor. Multimodal therapy should be employed and referral to a melanoma specialist familiar with immune and targeted-therapies is recommended.

Conflict of interest statement

The authors have no conflict of interest to report.

References

- Carlson Jr., J.A., Wheeler, J.E., 1993. Primary ovarian melanoma arising in a dermoid stage IIIc: long-term disease-free survival with aggressive surgery and platinum therapy. *Gynecol. Oncol.* 48, 397–401.
- Carvajal, R.D., Spencer, S.A., Lydiatt, W., 2012. Mucosal melanoma: a clinically and biologically unique disease entity. *J. Natl. Compr. Cancer Netw.* 10, 345–356.
- Cronje, H.S., Woodruff, J.D., 1981. Primary ovarian malignant melanoma arising in cystic teratoma. *Gynecol. Oncol.* 12, 379–383.
- Deshpande, A.H., Munshi, M.M., 2001. Primary malignant melanoma of the uterine cervix: report of a case diagnosed by cervical scrape cytology and review of the literature. *Diagn. Cytopathol.* 25, 108–111.
- Mousavi, A.S., Fakor, F., Nazari, Z., Ghaemmaghami, F., Hashemi, F.A., Jamali, M., 2006. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *J. Low. Genit. Tract Dis.* 10, 258–263.
- Myriokefalitaki, E., Babel, B., Smith, M., Ahmed, A.S., 2013. Primary malignant melanoma of uterine cervix FIGO IIa1: a case report with 40 months ongoing survival and literature review. *Gynecol. Oncol. Case Rep.* 5, 52–54.
- Siegel, R., Ma, J., Zou, Z., Jemal, A., 2014. *Cancer statistics, 2014*. *CA Cancer J. Clin.* 64, 9–29.
- Sugiyama, V.E., Chan, J.K., Kapp, D.S., 2008. Management of melanomas of the female genital tract. *Curr. Opin. Oncol.* 20, 565–569.