Case Report

Primary gynecologic melanoma: A report of two unusual cases

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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.

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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%
(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 immune-therapy 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.

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