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CASE REPORT

Amelanotic primary cervical malignant melanoma: A case report and review of literature

Jin-Lin Duan, Jing Yang, Yong-Long Zhang, Wen-Tao Huang

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Abstract

BACKGROUND

Primary malignant melanoma of the cervix (PMMC) is an extremely rare disease that originates from primary cervical malignant melanoma and frequently represents a challenge in disease diagnosis due to unclarified clinical and histological presentations, particularly those without melanin.

CASE SUMMARY

Here, we report a case of amelanotic PMMC, with a history of breast cancer and thyroid carcinoma. The patient was finally diagnosed by immunohistochemical staining and staged as IB2 based on the International Federation of Gynecology and Obstetrics with reference to National Comprehensive Cancer Network guidelines and was treated with radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. She then received combination therapy consisting of immunotherapy with tislelizumab and radiofrequency hyperthermia. She has remained free of disease for more than 1 year.

CONCLUSION

The differential diagnosis process reenforced the notion that immunohistochemical staining is the most reliable approach for amelanotic PMMC diagnosis. Due to the lack of established therapeutic guidelines, empirical information from limited available studies does not provide the rationale for treatment-decision making. By integrating 'omics' technologies and patient-derived xenografts or mini-patient-derived xenograft models this will help to identify selective therapeutic window(s) and screen the appropriate therapeutics for targeted therapies, immune checkpoint blockade or combination therapy strategies effectively and precisely that will ultimately improve patient survival.

Key Words: Primary cervical malignant melanoma; MelanA; Immunotherapy; Patient management; Case report

Core Tip: We report a case of unsuspected amelanotic primary malignant melanoma of the cervix (PMMC) with a history of breast cancer. The patient underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy, and then received radiotherapy combined with immunotherapy. She has remained free of disease for more than 1 year. The successful management of this patient underscores the critical role of routine immunohistochemical staining during cervical cancer diagnosis to exclude unsuspected PMMC, and adjuvant immunotherapy may be an option for PMMC.

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INTRODUCTION

Primary malignant melanoma of the cervix (PMMC) is extremely rare. Due to a lack of melanocytes in the cervix, PMMC represents a challenge in clinical diagnosis. Currently, there is no consensus or guidelines for the treatment and management of PMMC. In most cases, treatment follows the surgical criteria for cervical squamous cell carcinoma. PMMC can be managed postoperatively or preoperatively.

CASE PRESENTATION

Chief complaints

A 56-year-old woman presented to our hospital in December 2022 with one-day postmenopausal bleeding.

History of present illness

The surgery was planned by a multidisciplinary team and she underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy, and one lesion (2.8 cm × 1.5 cm × 1.3 cm) was observed in the lower end of the cervix and its section appeared white in color. Biopsies were further evaluated by pathological examination. The tumor had invaded into 1/2 layer of the cervical muscle wall, and the depth of tumor invasion in the cervix was approximately 6 mm. The endometrium, bilateral adnexa, lymph nodes, and vaginal stump were free of tumors.

History of past illness

Eighteen years ago, she was diagnosed with breast duct carcinoma, and she underwent radical left unilateral mastectomy and then right unilateral mastectomy in 2014. She additionally underwent thyroidectomy two years later due to thyroid carcinoma.

Personal and family history

Eighteen years ago, she was diagnosed with breast duct carcinoma, and underwent radical left unilateral mastectomy and then right unilateral mastectomy in 2014. She additionally underwent thyroidectomy two years later due to thyroid carcinoma.

Physical examination

Slight bulging of the anterior vaginal wall and posterior vaginal fornix was observed.

Laboratory examinations

Human papillomavirus screening was negative. Quantitative DNA ploidy analysis identified at least 3 heterotypic cells and the DNA index value was over 2.5. Unexpectedly, a routine serum chemistry panel and plasma tumor biomarker examination, including squamous cell carcinoma antigen, were all within normal limits.

Imaging examinations

Ultrasound findings revealed a hypoechoic area measuring approximately 14 mm × 15 mm × 12 mm with clear boundaries and irregular internal echoes were seen in the cervix. Magnetic resonance imaging suggested abnormal cervical morphology, with a high signal intensity of mixed T1WI (T1 weighted image) and T2WI (Figure 1A and B). Uneven reinforcement was observed after enhanced scanning (Figure 1C and D). Furthermore, colposcopy and cervical biopsy

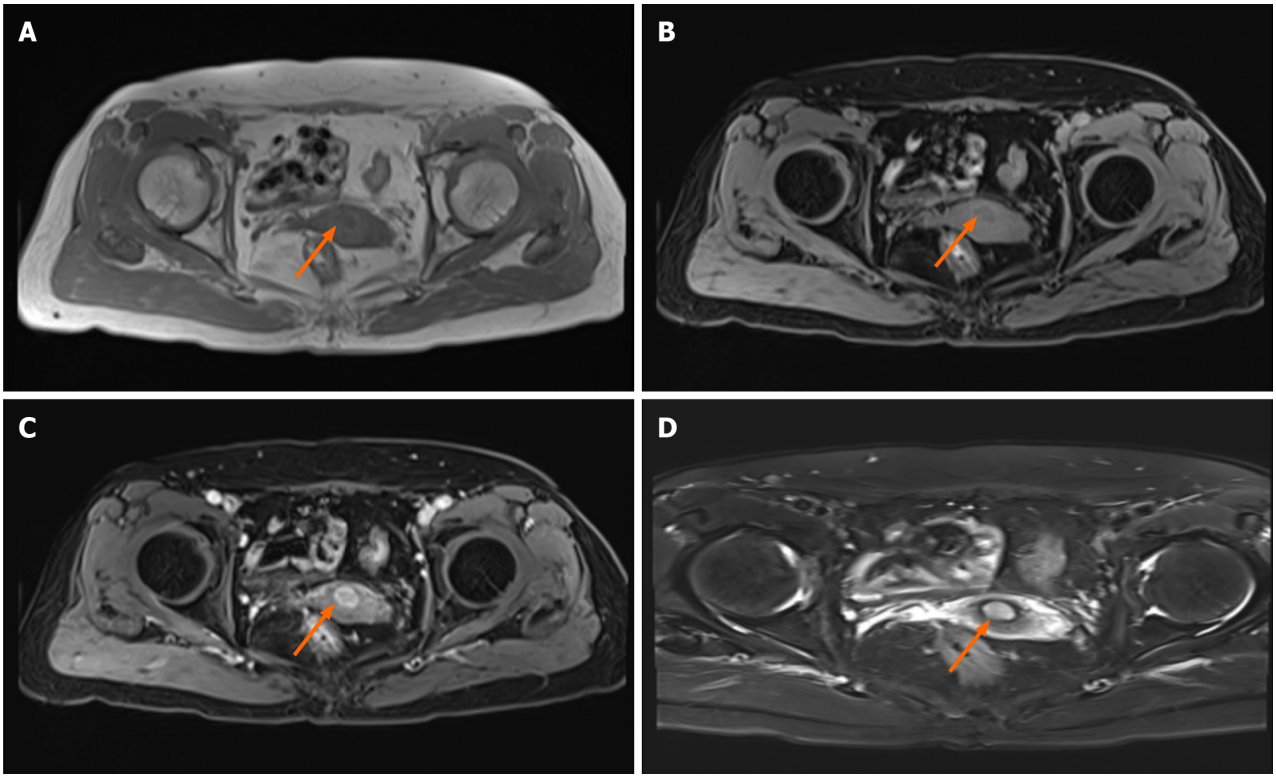

Figure 1 Pelvic magnetic resonance imaging. A: T1 weighted image (arrow); B: Fat-suppression T1-weighted image (arrow); C: T1WI lipocompression enhanced scan (arrow); D: T2WI lipocompression enhanced scan (arrow).

examination suggested small round cell malignancy, of which the tumor cells were arranged in a nest-like and cord-like pattern, with an epithelial-like morphology, significant atypia, minimal cytoplasm, deep staining and frequent mitotic activity (Figure 2).

MULTIDISCIPLINARY EXPERT CONSULTATION

The surgery was planned by a multidisciplinary team and the patient underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy.

FINAL DIAGNOSIS

Considering the negative expression of pan-Keratin (AE1/AE3) and GATA3, as well the histological findings, this generally rules out the possibility that the tumor originated from primary breast cancer. Negative p40 and p16 reactivity in resected tumors on immunohistochemical (IHC) staining excluded the possibility of primary cervical cancer. Stepwise serial diagnostic IHC staining of biomarkers related to common cancers was performed. Surprisingly, the cells were strongly positive for MelanA, S-100, SOX-10 and HMB45, the biomarker for cervical melanoma (Figure 3). Due to the lack of melanin observed in the lesion, primary cervical malignant melanoma was not considered initially. The patient was finally diagnosed with primary cervical malignant melanoma.

TREATMENT

Multiplex gene-panel testing indicated a genetic mutation of BRCA2 (exon11). She then received combination therapy consisting of the anti-PD1 antibody tislelizumab (200 mg, d1, q3w) and radiofrequency hyperthermia for 1.5 years.

OUTCOME AND FOLLOW-UP

The patient has undergone monthly follow-up visits. To date, she remains free of disease, without evidence of disease recurrence or metastasis for 1 year.

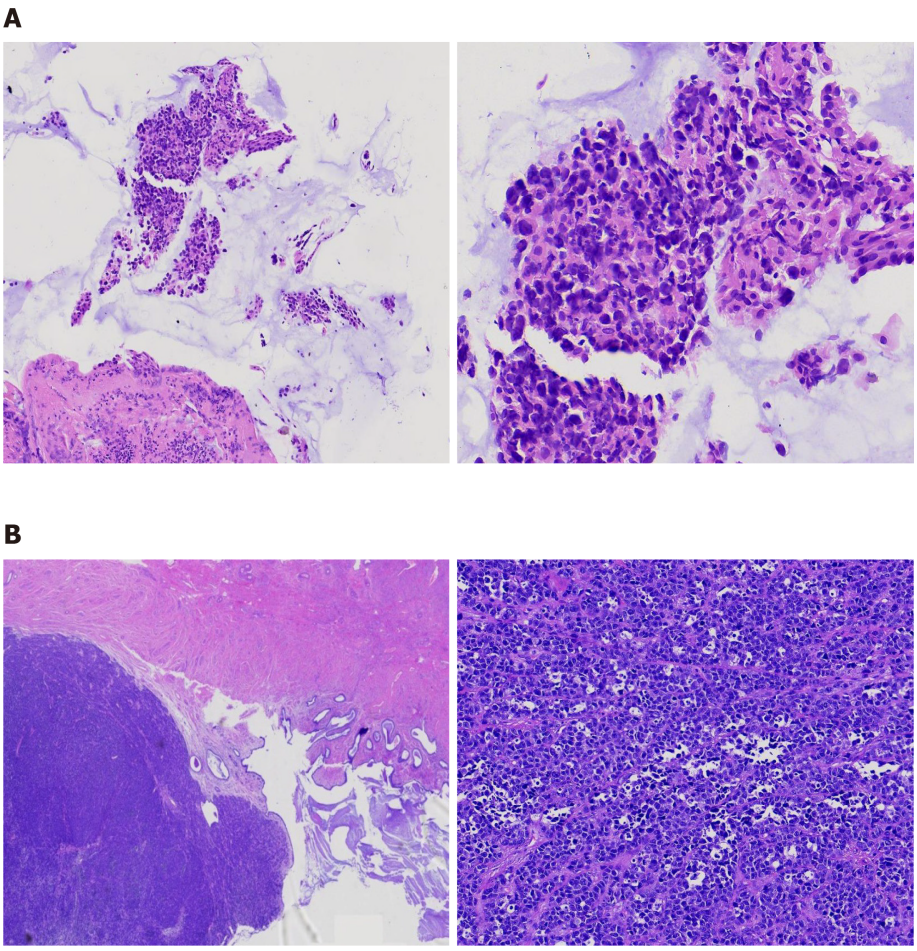

Figure 2 Histological examination showed small round cell malignancy with a high mitotic activity. A: Colposcopy and cervical biopsy; B: Resected biopsy specimen.

DISCUSSION

Primary cervical malignant melanoma represents an exceedingly uncommon tumor that can occur in the uterine cervix[1-4]. Since it was initially described as macroscopically "black cancer" of the cervix in 1889, only 149 cases have been reported to date[5]. The presence of melanin is one of the four criteria for the diagnosis of cervical melanoma[6]. Less than 20% of cases are, however, amelanotic and 3.5% cells in the cervical melanoma are melanin-containing cells compared with normal cervical epithelia[7,8]. Therefore, routine inclusion of IHC staining of combined S100 sensitivity, HBM45 specificity and MelanA staining is of great significance in facilitating the differential diagnosis of cervical malignancies without delays in situations where there is a lack of pigment. This is probably why IHC staining is more specific than Masson–Fontana staining[1,3]. Given that primary malignant melanoma frequently undergoes distant metastasis, excluding its origin from a primary cutaneous melanoma is a top priority for cervical melanoma diagnosis[9-12]. Both scanning and later positron emission tomography/computed tomography ruled out the presence of melanoma in other anatomic structures due to a distinct signal pattern from the paramagnetic properties of melanin[11,13]. This case was staged as IB2, without lymph node and distant metastasis, and she underwent regional lymph node dissection, although dissection of clinically negative regional lymph nodes is still controversial[14-18], indicating that a future study involving a larger sample size is necessary to determine the value of lymph node dissection in patients with PMMC.

Although melanoma is considered radio-resistant, the combination of ionizing radiation with hyperthermia provokes a systemic immune response and potentiates the efficacy of immunotherapy[19,20]. This case therefore received radiotherapy combined with immunotherapy, and the long-term effect is yet to be evaluated although she has been free of disease for 1 year. Notably, the combination of chemotherapy with either immunotherapy or radiotherapy has demonstrated a limited effect in patients with PMMC as previously reported[11,13,21,22]. Similar to melanoma, PMMC bears common driver mutations, such as BRAF and BRCA2, which can be therapeutically targeted. Our patient was found to have a BRAC2 mutation (exon11), ideally providing a therapeutic opportunity for treating this patient with the PARP inhibitor olaparib, which has been approved for BRCA1/2-mutated metastatic ovarian cancer and showed considerable survival benefit[23-26]. This agent may be an option if tumor relapse occurs in this patient in the future. Given the lack of consensus with respect to the management of MM due to disease rarity, it is impossible to conduct clinical trials with sufficient cases, and anecdotal evidence and empirical information from previous studies do not provide enough evidence on the impact of available treatment options[1,5]. With this in mind, it is therefore important to take advantage of new 'omics' technologies that lead to the understanding of the genetic and epigenetic landscape of individual PMMC to

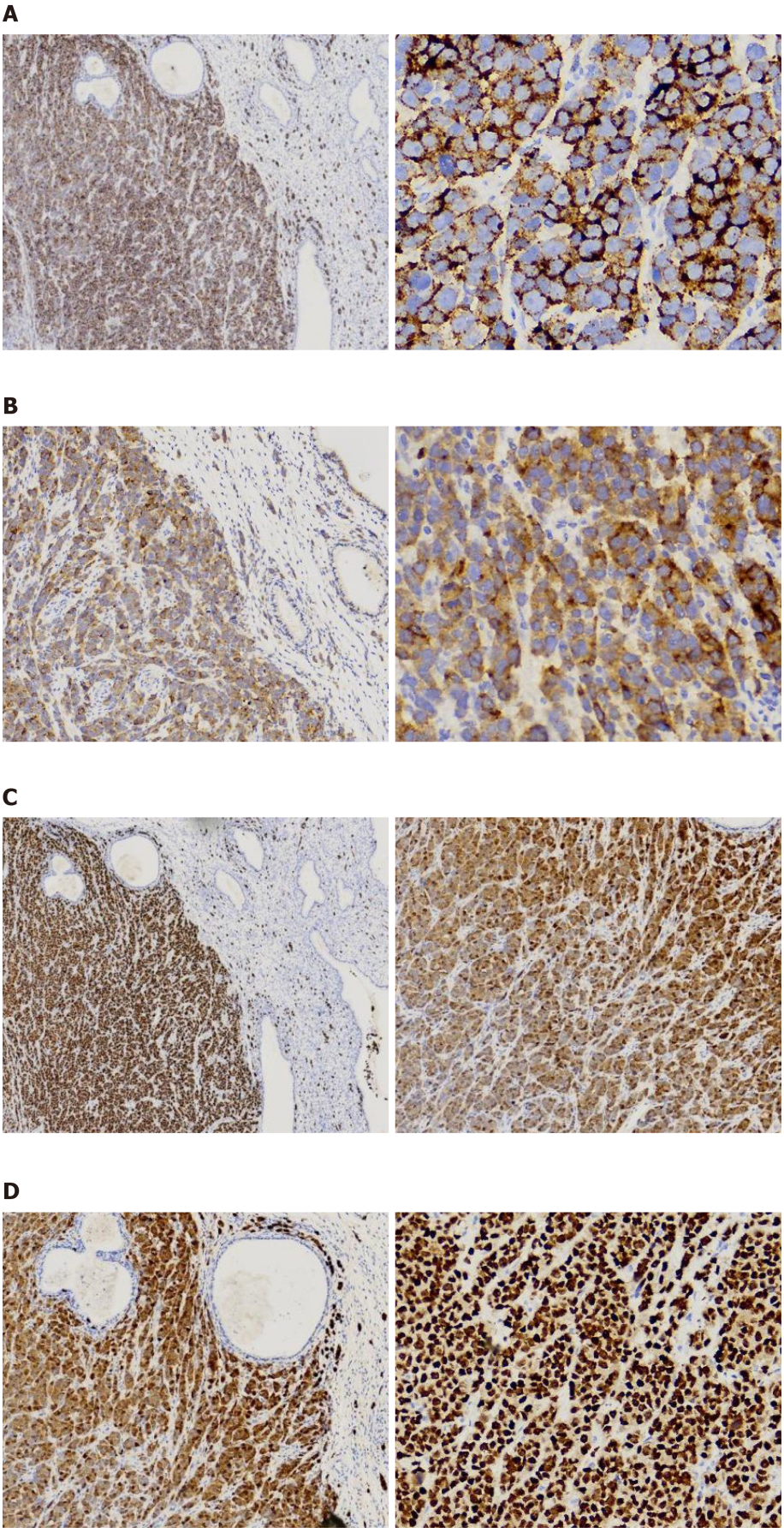

Figure 3 Immunohistochemical staining of resected biopsy specimen. A: HMB45; B: MelanA; C: S-100; D: SOX10. The tumors were positive for HMB45, MelanA, S-100 and SOX10. Scale bar, left, 100 μm; right, 400 μm.

optimize the potential of personalized medicine. On the other hand, patient-derived xenografts (PDXs) are powerful models in screening and selecting the correct therapeutics in the clinic[27-32]. A mini patient-derived xenograft (MiniPDX), which is based on capsule implantation in nude mice, can rapidly test drug efficacy within 7 days[33-37]. The application of these new models to PMMC will be extremely helpful in strengthening personalized treatment of PMMC.

CONCLUSION

The differential diagnosis process reenforced the notion that immunohistochemical staining is the most reliable approach for amelanotic PMMC diagnosis. Due to the lack of established therapeutic guidelines, empirical information from limited previous studies does not provide the rationale for treatment-decision making. By integrating 'omics' technologies and PDXs or mini-PDX models this will help to identify selective therapeutic window(s) and screen the correct therapeutics for targeted therapies, immune checkpoint blockade or combination therapy strategies effectively and precisely that will ultimately improve patient survival.

FOOTNOTES

Author contributions: Duan JL and Yang Y contributed to the histological examinations and collection of patient data; Duan JL and Yang Y assembled the data; Huang WT and Zhang YL performed data analysis and interpretation; Huang WT, Duan JL, and Zhang YL wrote the manuscript; All authors read and approved the final manuscript; Huang WT and Zhang YL confirm the authenticity of all the raw data; Duan JL and Yang J contributed equally to this work.

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