CASE REPORT

Primary malignant melanoma of the cervix: a rare disease

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SUMMARY

Malignant melanoma (MM) arising primarily in the cervix is exceedingly rare and has a poor prognosis. We report the case of a primary MM of the cervix in a 64-year-old woman with vaginal bleeding. She presented with a cervical amelanotic lesion which on biopsy rendered the diagnosis of MM. The patient was staged as International Federation of Gynecology and Obstetrics IIB and underwent Wertheim-Meigs hysterectomy followed by brachytherapy. One year later, she was diagnosed with a large pelvic relapse for which surgery was performed. She then presented with a vaginal relapse and an isolated hepatic lesion, both of which were proposed for surgery. The diagnosis of MM of the cervix is a clinical and pathological challenge due to its rarity and overlapping features. Cytology cannot accurately diagnose it. Moreover, amelanotic MMs must be distinguished from other poorly differentiated carcinomas by diagnosis that ultimately relies on immunohistochemical staining. Radical surgery is the only treatment showing predictive benefit.

BACKGROUND

Mucosal malignant melanoma (MM) has a low incidence and only 2% are diagnosed in the gynaecological tract.¹ Primary MMs of the cervix are rare with around 80 cases described.²

Diagnosing primary cervical MM is often difficult. Clinical presentation mimics other cervical malignancies, usually exhibiting discharge or abnormal bleeding.³ They can have an asymptomatic initial growth until the lesions ulcerate or become infected.⁴ Colposcopic observation can detect a coloured exofit lesion.⁵ Cervical screening tests like cytology are often incapable of detecting MMs because they are highly observer dependent and because of the rarity of the disease.⁶ Therefore, histological evaluation of the lesions is crucial, and immunohistochemical staining proves very helpful in differentiating lesions. Another important issue is to be certain that the lesion is not metastatic. Other primary sites must be excluded, like cutaneous, other mucosal or ocular. Staging is also important for prognosis and treatment, although frequently presenting in advanced stages. Most authors use the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer due to similar metastatic spreading. Tumor, Node, Metastasis (TNM) system does not specify staging for mucosal melanomas other than head and neck.^{7,8}

Figure 1 Colposcopy assessments in October 2014.

Mucosal MMs are usually coloured; however, in 35%–45% of the cases, they develop as colourless lesions, so they are called amelanotic MMs.⁹ Their identification involves a difficult clinical and pathological diagnosis. The differential diagnosis with other poorly differentiated squamous cell carcinomas, lymphomas or sarcomas must be attended.¹¹ Immunohistochemical staining is crucial in confirming the diagnosis, combining S100 sensitivity, HBM45 specificity and MelanA staining.²

Therefore, the rarity of this disease, the difficulty associated with the diagnosis and the lack of evidence regarding treatment make case reports a valuable tool in deciding patient management.

Figure 2 Colposcopy assessments in January 2015.

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Figure 3 Colposcopy assessments in January 2015, 18 days after figure 2.

We report the case of a 64-year-old woman diagnosed with a primary amelanotic cervical MM, FIGO IIB, treated with radical hysterectomy.

CASE PRESENTATION

A multiparous, HIV-negative, postmenopausal 64-year-old woman was attending a private gynaecologist due to a low-grade squamous intraepithelial lesion detected in screening cytology in August 2014. Medical history revealed arterial hypertension, adenomatous intestinal polyps and urinary effort incontinence. Gynaecological history showed two voluntary abortions and an endometrial polyp resection in 2012. The patient's mother died due to cutaneous MM.

A previous colposcopic evaluation was available, performed in October 2014, presenting with an atrophic cervix and no other findings (figure 1).

In January 2015, she presented with postmenopausal vaginal bleeding and dyspareunia. A transvaginal ultrasound reported a thickened endometrium (8×7 mm), and she was referred to the cervical pathology unit.

Figure 4 Microscopic examination showed a highly cellular neoplasm exhibiting a high mitotic activity (H&E).

Figure 5 Immunohistochemistry: the tumour cells were positive for HMB45.

INVESTIGATIONS

Colposcopy was reported as adequate, type 3 Transformation Zone (TZ) with a polypoid exofitotic pale lesion at 6 o'clock. This lesion was ulcerated and showed spontaneous bleeding, suggesting invasion, so a biopsy was performed (figure 2).

Microscopic examination showed a highly cellular neoplasm composed of epithelioid cells with round to oval hyperchromatic nuclei, prominent nucleoli and granular cytoplasm. The neoplastic cells exhibited a high degree of nuclear pleomorphism and mitotic activity. On immunohistochemistry, the tumour cells were positive for HMB-45, S100 protein and MelanA, and negative for cytokeratins. The diagnosis of MM was rendered.

The patient was referred to gynaecological oncology department, and the disease was staged with a thoracoabdominal CT and pelvic MRI. A follow-up colposcopy showed a noticeable increase in the lesion size (figure 3). MRI reported a cervical lesion in the posterior lip with 3.1×1.2×2.9 cm and suspected anterior parametrial extension. CT scan was unremarkable.

In March 2015, the patient was referred to Instituto Português de Oncologia do Porto, a Portuguese comprehensive oncology centre. The gynaecological evaluation reported a cervical exofitotic amelanotic and necrotic lesion, with 3 cm in diameter and suspected micronodular invasion of the right parametrium. A thorough evaluation of vaginal walls did not show any satellite

Figure 6 Immunohistochemistry: the tumour cells were positive for Melan-A.

Figure 7 Immunohistochemistry: the tumour cells were positive for S100 protein.

lesions. The patient was staged as a proximal FIGO IIB and underwent ^{18}F -FDG (fludeoxyglucose) positron emission tomography (PET) scan that showed no other hypermetabolic lesions. A second look of the samples in the pathology department confirmed the diagnosis (figures 4–7). The case was then discussed in a gynaecology multidisciplinary tumour board with the presence of dermatology, concluding on a primary melanoma of the cervix.

TREATMENT

A radical surgical approach was proposed to the patient with her acceptance. On 31 March 2015, she underwent a Wertheim-Meigs hysterectomy with an uneventful recovery. Gross pathological examination showed a lesion measuring 85x45x40 mm (figure 8). The final histopathology report verified the presence of a nodular MM with ulceration (Breslow thickness of 13 mm). There was a brisk lymphocytic response, and the mitotic count was up to 54 per 10 high-power fields. There were no features of regression, microsatellite lesions or perineural invasion. Lymphovascular invasion was identified. The tumour invaded the vagina and was resected with a 4 mm clear peripheral microscopic cuff margin. All of the 15 lymph nodes and parametrial soft tissue were free of disease.

The patient was observed in a postoperative gynaecology consultation, in May 2015, where an imagiological restaging was ordered, showing no distant metastasis and vaginal brachytherapy was proposed in the tumour board due to close margins. In the first radio-oncology evaluation, in June 2016,

a solid nodule of about 1 cm was observed in the vaginal vault, and the biopsy confirmed early relapse. PET-CT showed isolated uptake on the biopsied nodule, and in July 2015 resection was performed with a deep 1 mm clear microscopic margin. After discharge, she underwent brachytherapy that was completed in September 2015.

OUTCOME AND FOLLOW-UP

The patient maintained surveillance at our institution. In May 2016, she presented with a pigmented vaginal lesion that was biopsied revealing reactive pigmentation of basal keratinocytes. In July, she was admitted to the gynaecology ward due to abdominal pain, emesis and constipation. Abdominal radiography showed small-bowel distension and air-fluid levels. The patient presented with *de novo* anaemia (9.3 mg/dL), a slightly elevated lactate dehydrogenase (LDH) (G1, ULN (Upper limit of normal) = 248 U) and no other relevant analytical findings. Symptoms were controlled after medical treatment. A PET-CT showed a large pelvic mass with small bowel invasion and several hypermetabolic lombo-aortic lymph nodes. In September 2016, she underwent enterectomy and mass resection with no residual disease. Gross examination revealed a 60 mm intestinal ulceroinfiltrative lesion. Histopathological examination confirmed it to be a metastatic MM with free surgical resection margins. In December, she presented with a suspected vaginal relapse, and a PET-CT showed an isolated hepatic lesion. The tumour board proposed resection of both lesions.

DISCUSSION

MMs can affect other locations outside the skin, and mucosal melanomas are a rare example. They can be found in oral, oesophageal, gastric, anal, gynaecological mucosa and others.¹ However, they represent less than 1.5% of all MM cases because cutaneous forms are the most prevalent.¹² Mucosal MM are more frequent in women, probably due to gynaecological MM,¹³ and these arise mostly in the vulva and vagina. Primary cervical MM is a very rare entity, with 78 cases reported in the literature.² Contrary to cutaneous melanomas, little is known about the genetic predisposition of mucosal MM, although it has been shown to develop in a familial setting.¹⁴

Mucosal melanomas, including cervical MM, do not have established treatment guidelines because of its rarity. However, it has become common ground that an optimal surgery is the most important step. Radical hysterectomy with wide margins and regional lymphadenectomy are the preferred approaches.^{15–17} Chemotherapy and radiation have been used with no proven benefit. Radiation therapy is often reserved for unsatisfactory surgical margins, locally advanced disease, involved lymph nodes

Figure 8 Gross examination of the surgical specimen showing a polypoid pale lesion in the posterior quadrants of the cervix.

or palliative intent, as MMs are usually radioresistant.¹⁸ Conventional MM chemotherapy offered some objective responses but with no survival benefit.¹⁶ Immunotherapy could be a treatment option in the future.

Cervical MM usually presents as locally advanced and less frequently as stage IV disease. Nonetheless, prognosis is very poor due to tumour aggressiveness, local relapse, frequently unresectable disease and poor outcome with systemic or radiation therapy. The median overall survival of published reports (78 cases) was 12 months (0.1–168 months) with two long survivors (13 and 14 years). Most of the women died 3 years after diagnosis.²

Learning points

- Primary melanoma of the cervix is an exceedingly rare disease and frequently a hard one to diagnose due to uncharacteristic clinical and histological presentation.
- Differential diagnosis between primary and secondary cervical malignant melanomas (MMs) must be made evaluating other more common locations for primary MMs.
- Optimal radical surgery is the best approach for these tumours. Close follow-up is necessary for early diagnosis and treatment of disease relapse. Chemotherapy and radiotherapy, with variable and unpredictable outcomes, should be used with palliative intent and to control symptoms.
- Referral to a specialised centre and inclusion in clinical trials are crucial to adequately treat and follow-up mucosal MMs.

Contributors All authors made a substantial contribution for the writing of this case report, namely: IJ was the main responsible for the conception and planning of this case report. He substantially reviewed available literature, started and accomplished the report draft, compiled available data, and interpreted and discussed important data integrating it with current literature. He comprehensively and critically reviewed the final draft, ensuring the truth and integrity of all the information. SDC actively contributed for the acquisition and interpretation of data, namely regarding pathology, and helped writing the final draft. She was also responsible for reviewing the literature and appraisal of scientific contents. She acquired some of the figures proposed for publishing and interpreted them, integrating all available data with their information. She comprehensively and critically reviewed the final draft, ensuring the truth and integrity of all the information. VP is one of the gynecologists of the department responsible for the reported treatment. She helped from the beginning with the conception and design of the report and critically adjusted the gynaecological information and integrated it with the remaining data. She helped acquiring and building the rationale behind this report and participated in the discussion of this case among the other authors before translating it into this draft. She comprehensively and critically reviewed the final draft, ensuring the truth and integrity of all the information. AR was responsible for coordinating the work and structuring it into the final report. She analysed all data,

critically evaluated the scenarios and revised the final draft. She conducted major changes in the structure of the initial design helping the group of authors to better organise the information. She comprehensively and critically reviewed the final draft, ensuring the truth and integrity of all the information.

Competing interests None declared.

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REFERENCES

- 1 Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol* 2007;56:828–34.
- 2 Pusceddu S, Bajetta E, Carcangiu ML, et al. A literature overview of primary cervical malignant melanoma: an exceedingly rare cancer. *Crit Rev Oncol Hematol* 2012;81:185–95.
- 3 Khurana A, Jalpota Y. Primary malignant melanoma of the uterine cervix. *Indian J Pathol Microbiol* 2009;52:575–6.
- 4 Yücesoy G, Kus E, Cakiroglu Y, et al. Primary malignant melanoma of the cervix: report of a case. *Arch Gynecol Obstet* 2009;279:573–5.
- 5 Mordel N, Mor-Yosef S, Ben-Baruch N, et al. Malignant melanoma of the uterine cervix: case report and review of the literature. *Gynecol Oncol* 1989;32:375–80.
- 6 Uzüm N, Köse F, Ataoğlu O. Metastatic malignant melanoma of the uterine cervix: first diagnosed on liquid-based cytology. *Diagn Cytopathol* 2008;36:769–72.
- 7 Chua S, Viegas OA, Wee A, et al. Malignant melanoma of the cervix. *Gynecol Obstet Invest* 1989;27:107–9.
- 8 Liu Z, Wang H, Zhang X, et al. Primary malignant melanoma of the cervix: a case report. *Oncol Lett* 2014;8:2661–3.
- 9 Tomicic J, Wanebo HJ. Mucosal melanomas. *Surg Clin North Am* 2003;83:237–52.
- 10 Deshpande AH, Munshi MM. Primary malignant melanoma of the uterine cervix: report of a case diagnosed by cervical scrape cytology and review of the literature. *Diagn Cytopathol* 2001;25:108–11.
- 11 Pusceddu S, Bajetta E, Buzzoni R, et al. Primary uterine cervix melanoma resembling malignant peripheral nerve sheath tumor: a case report. *Int J Gynecol Pathol* 2008;27:596–600.
- 12 Chang AE, Karnell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. the American college of surgeons commission on cancer and the american cancer society. *Cancer* 1998;83:1664–78.
- 13 McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the US. *Cancer* 2005;103:1000–7.
- 14 Cazenave H, Maubec E, Mohamdi H, et al. Genital and anorectal mucosal melanoma is associated with cutaneous melanoma in patients and in families. *Br J Dermatol* 2013;169:594–9.
- 15 Kristiansen SB, Anderson R, Cohen DM. Primary malignant melanoma of the cervix and review of the literature. *Gynecol Oncol* 1992;47:398–403.
- 16 Myriokefalitaki E, Babbal B, Smith M, et al. Primary malignant melanoma of uterine cervix FIGO IIa1: a case report with 40 months ongoing survival and literature review. *Gynecol Oncol Case Rep* 2013;5:52–4.
- 17 Piura B. Management of primary melanoma of the female urogenital tract. *Lancet Oncol* 2008;9:973–81.
- 18 Mousavi AS, Fakor F, Nazari Z, et al. Primary malignant melanoma of the uterine cervix: case report and review of the literature. *J Low Genit Tract Dis* 2006;10:258–63.

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