CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Blue nevus-like melanoma of the uterine cervix. Case report and review of the literature

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Abstract

We present the clinical and pathological aspects of a patient diagnosed with a very rare tumor, a blue nevus-like melanoma of the uterine cervix. The patient turned to our Service for a second opinion regarding a cervical polyp causing vaginal bleeding, polyp which has been excised in another Hospital and interpreted initially as a pleomorphic sarcoma. In the presentation, we emphasize upon the stages of solving a difficult diagnosis, pathological description and treatment of these rare, aggressive tumors with poor prognosis, which represent the fundamental precondition in order to formulate the best therapeutic strategy.

Keywords: malignant melanoma, uterine cervix, blue nevus, blue nevus-like melanoma.

Introduction

Originating in the paramesonephric ducts, the uterine cervix is an organ, which is normally devoid of melanocytes. However, due to an embryologic migration of cells from the neural crest, at this level, the whole range of pigmentary lesions can be encountered, from lentigo-type benign lesions to malignant melanoma (MM) [1].

Pigmented lesions of the uterine cervix are usually accidental discoveries of no clinical relevance [2] but which nonetheless require thorough investigation in order to differentiate them from a MM, a very difficult task with vital importance for the patient's prognostic.

One morphological entity that can pose particular problems of differential diagnosis is the blue nevus [3]. The difficulty of the diagnosis is heightened by the fact that, unlike most benign melanocytic lesions that are stable over time, sometimes the blue nevus may evolve into or may be associated with a MM, constituting the so-called "blue nevus-like melanoma" (BNLM) [2].

BNLM is a controversial term, first used by Allen & Spitz to describe blue nevus-like lesions, which led to metastases or even resulted in the patient's death [4].

The most common localization of BNLM is at the level of the scalp, followed by the face, the buttocks and the thorax. In the genital sphere, such lesions are extremely rare and lead to a severe prognosis [5].

In this paper, we present the clinical and pathological aspects of a patient diagnosed with BNLM of the uterine cervix, which was initially suspected to be a poorly differentiated sarcoma and BNLM of the uterine cervix, subsequently diagnosed after surgical treatment and immunohistochemistry.

Case presentation

A 51-year-old patient, nulliparous, with no pathological or family history regarding melanomas, turned to us with the diagnosis of "pleomorphic sarcoma" of the uterine cervix, established by a different service, as a result of excision of a cervical polyp, recently complicated with hemorrhages. During the gynecological examination, the uterine cervix presented an infiltrative lesion of approximately 4/3 cm, of black-bluish color, with irregular margins, variable pigmentation, including depigmented areas; the lesion did not invade the vaginal cul-de-sac, the uterus or the parameters. The presence of satellite lesions was not observed.

The general clinic examination, as well as the other imagistic investigations did not show any suspicious lesions in the lungs, the liver, the spleen, the kidneys or the retroperitoneal structures. No intra-abdominal or inguinal lymphadenopathies were revealed. Endometriosis lesions, a blue nevus or a primitive melanoma of the uterine cervix were taken into consideration.

The re-biopsy of the uterine cervix established the diagnosis of MM (Figure 1, a–d).

Given the serious prognosis of the melanoma, in general, it was decided to proceed with a radical surgical intervention, and a Wertheim hysterectomy was conducted. During the procedure, no advanced intra-abdominal disease was observed, neither at the level of the parameters or at the level of other organs (Figure 2, a and b).

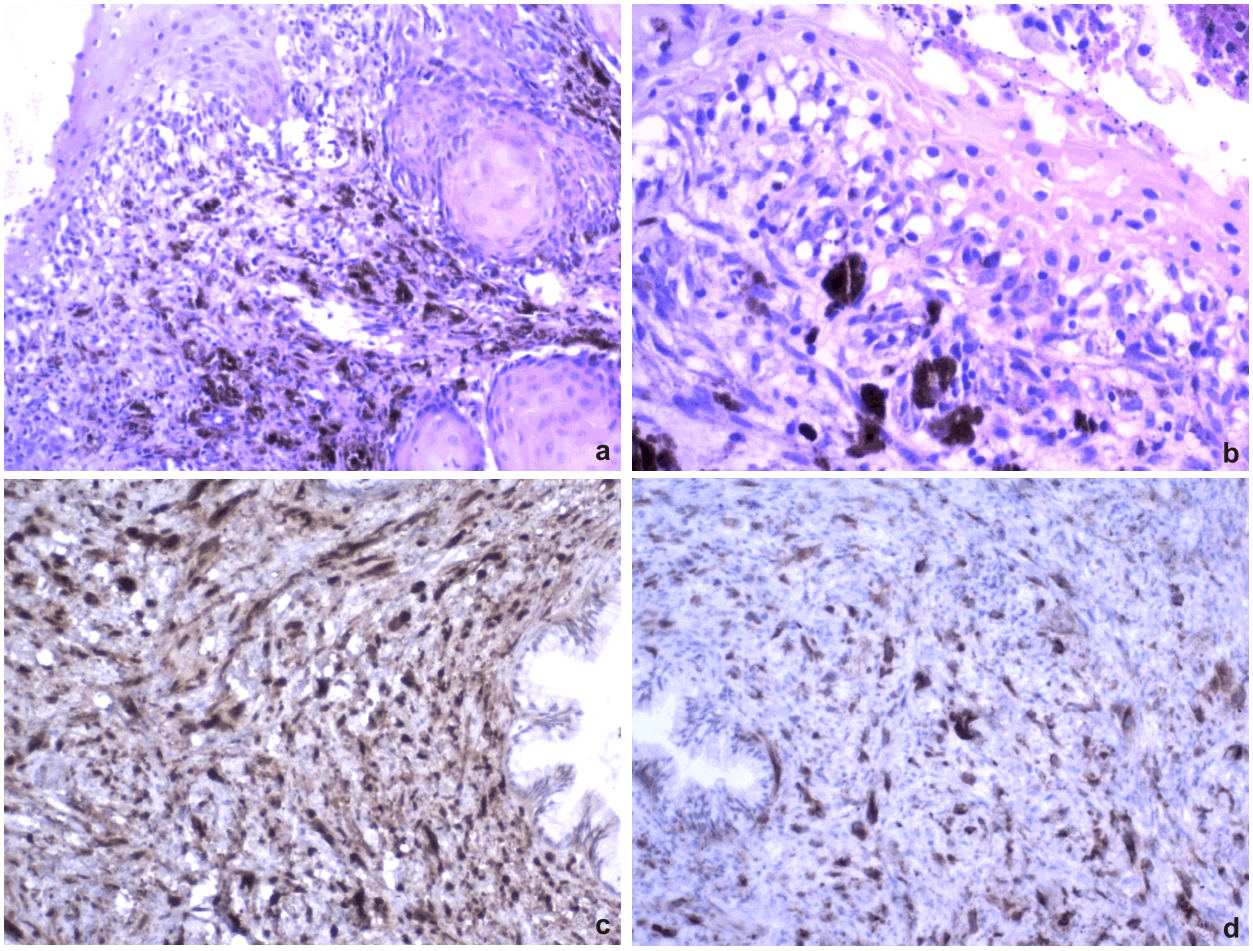

Figure 1 – ***Cervical melanoma (re-biopsy): (a and b) Infiltrative tumor proliferation from fusiform cells, with intracytoplasmic melanic pigment, with large nuclei; (c) S100 positive; (d) HMB45 positive. Hematoxylin–Eosin (HE) staining: (a and b) ×100. Anti-S100 antibody immunomarking: (c) ×100. Anti-HMB45 antibody immunomarking: (d) ×100. HMB45: Human melanoma black 45.***

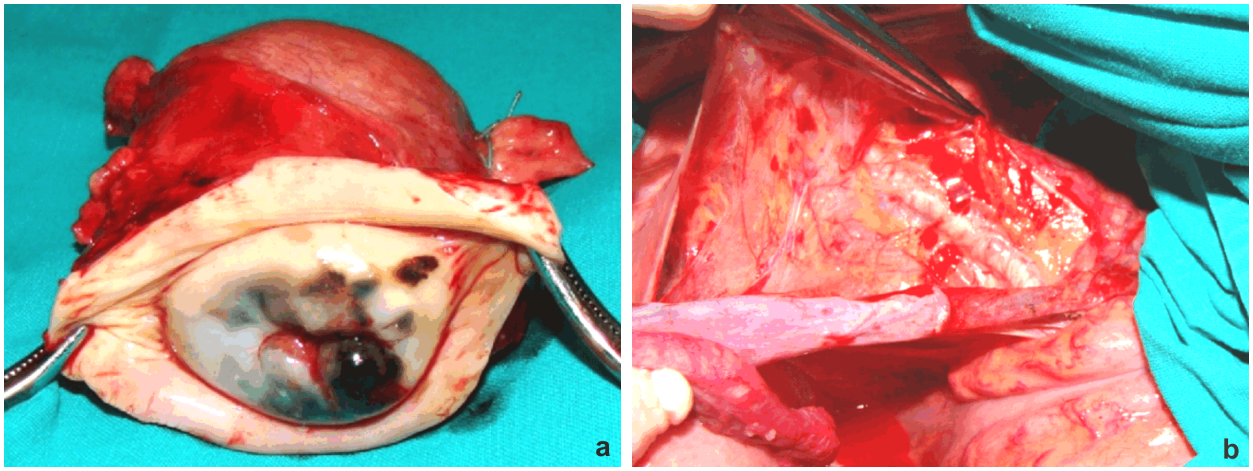

Figure 2 – ***(a) Malignant melanoma of the uterine cervix – appearance of the surgical specimen; (b) Intraoperative aspect of the right iliac fossa, with macroscopic dark-colored adenopathies that have not been histopathologically confirmed as secondary determinations.***

Surprisingly, the histopathological (HP) examination of the surgical specimen did not reveal specific characteristics of the MM, but identified a subepithelial proliferation of fusiform cells, at the level of the uterine cervix, with strong melanin focal pigmentation, with no implication of the junction. HP diagnosis was cervical cellular blue nevus (Figure 3, a–c). The parameters, the vaginal tranches (1.4 cm minimal length of the specimen) and all surgical

resection margins were tumor-free. Also, all 28 pelvic lymph nodes resected were tumor-free.

In order to solve the diagnosis, the Lab asked for the paraffin blocks of the cervical polyp excised initially by a different service, in order to be re-interpreted within our Institution.

HP analysis revealed a tumor proliferation, with a cervical location made up of atypical epithelioid and spindle-shaped cells, with pleomorphic nuclei, some with nucleoli and others with eosinophilic inclusions. The cytoplasm of these cells was eosinophilic, containing brown granular pigment, with typical and atypical mitoses and increased mitotic index (8 mitoses/mm^2) and focal points of hemorrhage and tumor necrosis. The tumor cells were S100 positive, c-kit and human melanoma black 45 (HMB45) positive. No images of angio-lymphatic or perineural invasion within the examined material were found. In conclusion, this polyp presented the aspect of a MM (Figure 4, a–d).

Hence, correlating the two HP results, the final diagnosis of BNLM of the uterine cervix was established.

It was not possible to establish a correct staging, given the fragmented biopsy specimen containing the malignant lesion. Clinically, the stage was established as stage I, at most stage II. As all margins were wide and free and there was no vascular or lymphatic space invasion, and all lymph nodes were free, the patient was not recommended any adjuvant therapy. She was only clinically monitored and frequent and close imaging was conducted.

One year after surgery, the patient presented multiple metastases of MM in the lungs, the sternum and the ribs, confirmed by biopsy, v-Raf murine sarcoma viral oncogene homolog B V600 mutation (*BRAF-V600*) positive. There were no clinical and imagistic signs of local or regional recurrence. Treatment with Dacarbazine was initiated. The patient deceased one year and eight months after the procedure.

Discussions

BNLM represents a rather rare lesion with a poor prognostic [4].

Today, the term is used to describe the malignant modifications which appear in a cellular blue nevus [2], the melanoma developed on the scar of an excised blue nevus [6], the melanoma with a cytoarchitecture resembling the cellular blue nevus, but which appears *de novo*, or the melanoma with a benign residual component of cellular blue nevus [6].

From a HP point of view, BNLMs are characterized by: high mitotic rate (more than 2 mitotic figures/mm^2), abnormal mitoses, vascular invasion, hypercellularity, expansive growth, atypicality and cellular pleomorphism, extended necrosis, with palisading cells around the areas affected by necrosis. Usually, there is a sharp demarcation between benign blue nevus lesion and the MM [7].

In the case of our patient, this HP characteristic might explain the lack of the malignant component from the hysterectomy specimen through its complete removal during the first intervention and re-biopsy.

At present, there is no data regarding the incidence of these lesions at genital level.

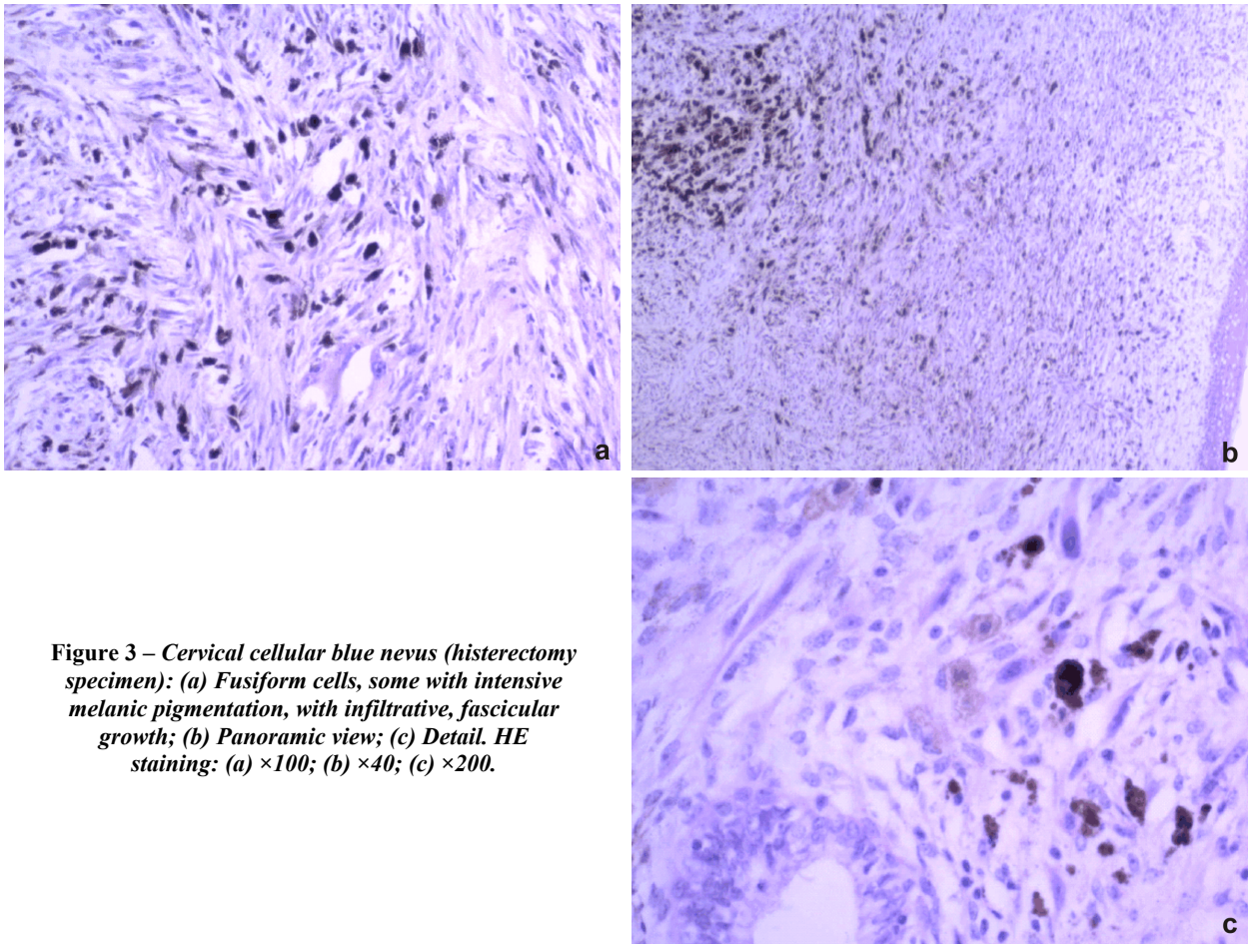

Figure 3 – ***Cervical cellular blue nevus (histerectomy specimen): (a) Fusiform cells, some with intensive melanic pigmentation, with infiltrative, fascicular growth; (b) Panoramic view; (c) Detail. HE staining: (a) ×100; (b) ×40; (c) ×200.***

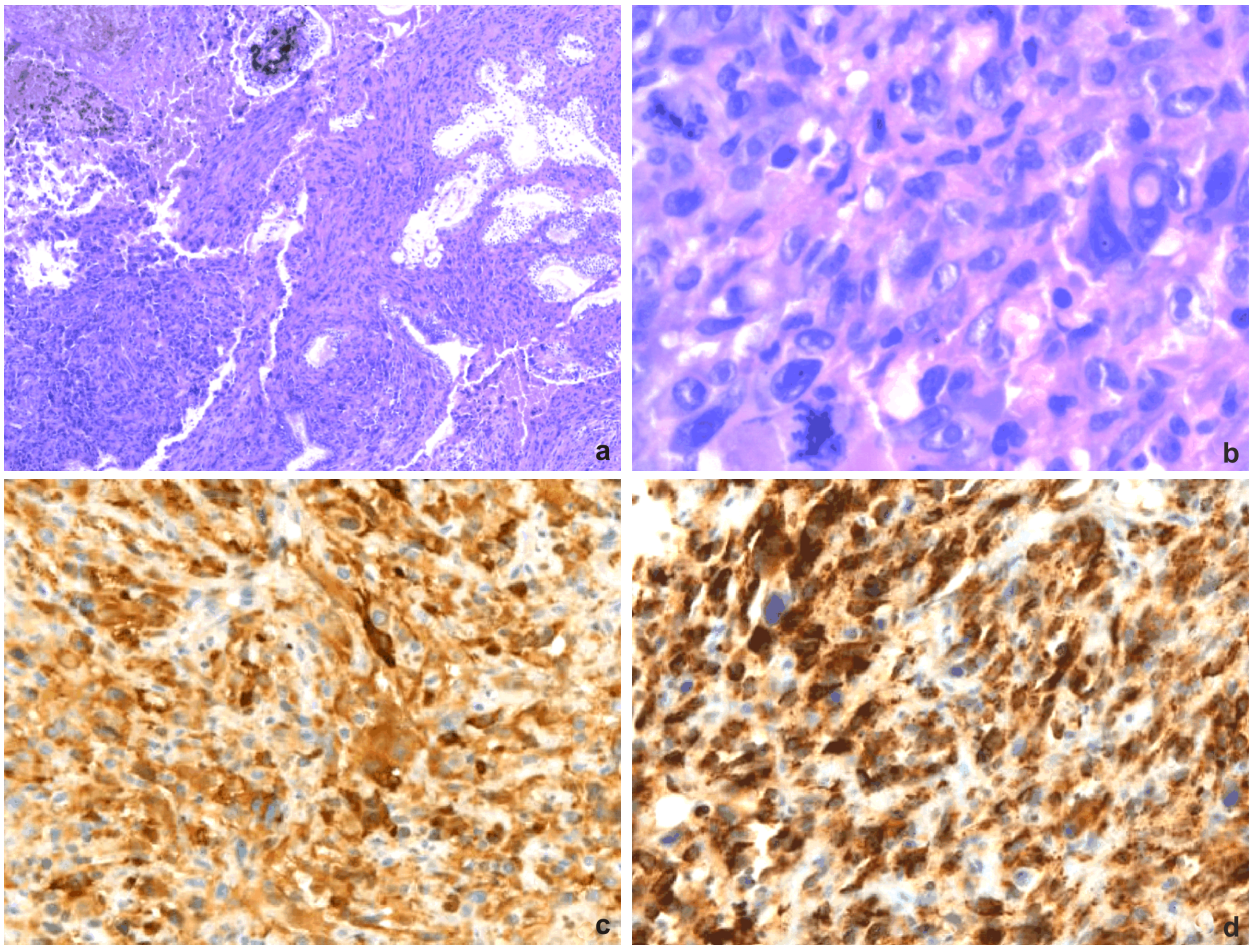

Figure 4 – ***Malignant melanoma developed in the context of a cellular blue nevus of the uterine cervix (polyp specimen): (a) Solid areas of atypical, epithelioid and fusiform cells, with hemorrhagic focal points and tumoral necrosis; (b) Mitoses and atypia; (c) S100 positive; (d) HMB45 positive. HE staining: (a) ×100; (b) ×400. Anti-S100 antibody immunomarking: (c) ×400. Anti-HMB45 antibody immunomarking: (d) ×400. HMB45: Human melanoma black 45.***

Parthenogenesis of the melanic cervical uterine lesion has not been yet elucidated. Some authors consider the hormonal factor to have an influence [8, 9], some take into account the genetic factors [10–13] and others emphasize the role of human papillomavirus (HPV) infection and primary gynecological MM development [14]. HPV subtype 16 was found in two cases of vulvar MM, and it is likely that this could influence the melanocytes in promoting cancer [14].

BNLM cases reported in specialized literature were very aggressive, and the majority developed metastases, which led to the death of the patient [15].

Literature describes cases of vulvar MM coexisting with blue nevus-type lesions, at the level of the uterine cervix or a coexisting MM and blue nevus of the uterine cervix [16]. The patients develop multiple metastases within less than three years from the diagnosis [15–17].

In 1998, Spatz *et al.* described the case of a patient with malignant blue nevus of the vagina, complicated with ovarian metastases 15 years after the initial diagnosis [7].

Given the first diagnosis of pleomorphic sarcoma, we took into consideration other non-pigmented malignant primary lesions like sarcomas (especially fusocellular sarcoma like leiomyosarcoma, and rhabdomyosarcoma), carcinosarcoma or undifferentiated carcinoma, lesions that have the well-known ability of mimicking the metastatic melanoma aspect on standard Hematoxylin–Eosin (HE) morphological examinations [6]. This possibility was ruled out by immunohistochemistry, which revealed positive for S100 and HMB45, sealing the final diagnosis. Metastatic lesions, such as clear cell renal carcinoma, lung adenocarcinoma or MM with other primary localization were excluded based on clinical examination, imaging and patient history. Possible benign conditions excluded were endometriosis, hemangioma and cervical melanosis.

Currently, there is no consensus regarding the best treatment of MMs of the uterine cervix. Nonetheless, surgical treatment is regarded as the leading option. Many authors prefer radical hysterectomy, joint with superior colpectomy and pelvic lymphadenectomy [1]. Some authors opt for total pelvic exenteration, with good long-term results [8].

The primary aim of the surgical intervention in the case of our patient was to obtain negative margins. There are authors who recommend margins of at least 2 cm in the case of melanomas of the uterine cervix [18, 19].

The role of radiotherapy in genital melanomas has not been clearly established yet, but it was proven that adjuvant radiotherapy can reduce the tumor dimension. Despite the reduced radiosensitivity of these tumors, external and intracavitary radiotherapy is indicated if satisfactory surgical margins were not obtained, in case of positive lymph nodes, parametrial invasion, or as palliative treatment in case of inoperable tumors [20–22].

Up to present, no chemotherapeutic regimen was able to substantially reduce the recurrence rate. Dacarbazine

was indicated in advanced illnesses, with efficiency up to 20% [20]. Other associative formulas of cytostatic drugs were experienced, but with modest results.

Most probably, this is due to the late discovery of the malignant component. These types of melanomas have an aggressive conduct and a prognosis resembling melanomas with a thickness over 4 mm, corresponding to stage IIB *American Joint Committee on Cancer* (AJCC) [7].

According to *International Federation of Gynecology and Obstetrics* (FIGO) staging of cervical cancer, our patient was staged IB1. The average survival rate at five years reported in the literature for such patients is very low: less than 40% in stage I and 14% in stage II [15].

Conclusions

BNLMs represent rare entities, which are currently not well understood and show unpredictable conduct. The location in the uterine cervix of such a tumor represents an exception, poses grand difficulties of diagnosis and treatment and leads to a poor prognosis, which is most probably due to the late discovery.

Disclosure of interests

The authors report no conflict of interests. The authors alone are responsible for the content and writing of the paper.

Informed consent for publication

The patient has consented for photos to be made and to publication using the data from her medical file.

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Received: September 10, 2019 *Accepted: January 21, 2020*