CLINICAL CASE

VULVAR MELANOMA – THERAPEUTIC CONSIDERATIONS

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ABSTRACT

Melanoma can develop both on the skin and in the mucosa at different levels: respiratory, gastrointestinal or genital, due to the melanocyte content of these tissues. In most cases, the prognosis of melanoma at the mucosal level has a much worse prognosis compared to that for melanoma at the tegument level. Symptoms described by patients with vulvar melanoma include bleeding, itching, vaginal discharge, dyspareunia or a palpable / visible tumor formation. We present the case of a 56-year-old, presented to our service with macula about 3.5 cm in diameter, dark brown color, and irregular edges, located at the level of the upper pole of the vulva.

KEYWORDS: *vulvar melanoma, mucosal melanoma, Breslow index, adjuvant therapies, Interferon alfa-2b*

INTRODUCTION

Melanomas can develop both on the skin and in the mucosa at different levels: respiratory, gastrointestinal or genital, due to the melanocyte content of these tissues.

The totality of the melanomas that have the primary site in the mucous membranes accounts for only 1% of the total malignant melanocyte tumors [1]. In terms of the frequency of vulvar cancers, vulvar melanoma ranks second in their frequency, accounting for 10% [2]. Melanomas that develop at the vulvar level are the most common of the melanomas of the mucous membranes and, in turn, account for 95% of all melanomas of the mucosa of the uro-genital tract in the female sex [3]-[7].

In most cases, the prognosis of melanoma at the mucosal level has a much worse prognosis compared to that for melanoma at the tegument level. At present, the etiopathogenesis of these melanomas is not fully known due to the fact that they are rarely encountered in medical practice, with a unique morphopathology and clinical manifestations that are difficult to interpret depending on the anatomical segment involved, so the appropriate management data for these malignancies are limited.

CASE PRESENTATION

We present the case of a 56-year-old woman from the urban area, non-smoking, with HTA, presented to our service with a tumor formation about 3.5 cm in diameter, dark brown color, and irregular edges, located at the level of the upper pole of the vulva. Our patient is a dressmaker, she has blue eyes, blonde hair and

the skin of phenotype 2. The patient's anamnesis showed no personal pathological history of skin cancer, or any heredocolateral history of malignant melanoma. Except the skin lesion, physical exam revealed no other abnormal findings. The laboratory tests were normal.

On clinical exam of the skin we found: macroscopically, the tumor formation had a diameter of about 3.5 cm, irregular edges, dark brown color, unrelated, with consistency similar to peritumoral tissue, with no signs of ulceration or infection (Figure 1).

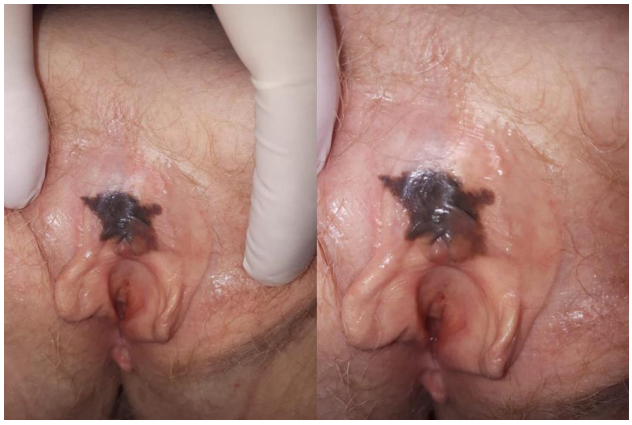

Figure 1 – The macroscopically view of the tumor formation

Punch-biopsy was performed in order to diagnose the tumor formation with certainty. The histopathological examination established the diagnosis of Melanoma vulvar, Clark III, extensively in the surface with the radial growth phase (Figure 2). The Breslow index was 2.1 mm. The excised piece comprises melanocyte proliferation, with the radial growth phase with atypical melanocytes arranged slowly. The mitotic activity index was set at 5 mitoses/mm^2. No perivascular or perineuronal intoxication was determined.

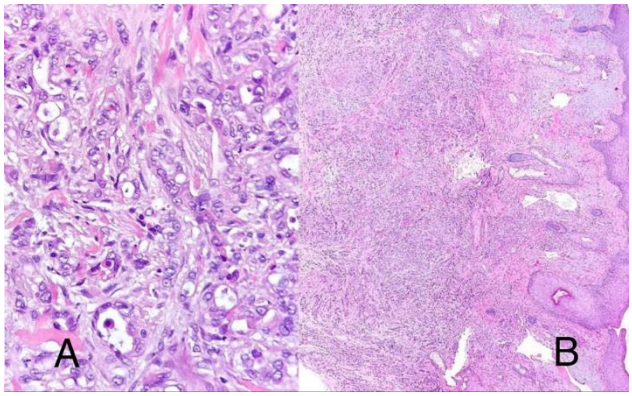

Figure 2 – Histopathological examination of the tumor formation

The next step was to perform a CT examination for 4 regions of the head, chest, abdomen and pelvis to determine if there were metastases. There was no evidence of secondary determination and oncology evaluations established therapeutic management, giving the indication for the intervention of curative excision of the tumor with bilateral lymphadenectomy of the inguinal femoral lymph nodes was decided. The difficult anatomical localization of the tumor, with the need for oncological safety margins over 2 cm, led to partial vulvectomy, without clitoral and urethral involvement. Adjuvant therapy included Interferon alfa-2b, at a dose of 15 MU/m^2 per day for 5 days a week for 4 weeks, then 9 MU/m^2 three times a week at present, with the plan to continue with this dose up to 48 weeks.

Currently, the patient continues adjuvant therapy with Interferon and shows no signs of relapse or distant dissemination.

DISCUSSIONS

Although vulvar melanoma is a rare disease commonly encountered in medical practice, it is one of the most common non-squamocellular malignant histopathological diagnoses described at vulvar level [8]. Differential diagnosis of vulvar pigmentation lesions includes, common lesions, such as: physiological/ postinflammatory hyperpigmentation, viral origin condylomas (HPV), squamocellular carcinomas, malignant nevi, angiokeratoma; lesions less commonly encountered, such as: lentigo vulvar, lichen planus, atypical melanocytic nevi, varicose veins; and very rare lesions, such as: pigmented basal cell carcinoma, acanthosis nigricans and papillary hidradenoma. Thus, any vulvar pigmented lesion should be subjected to rigorous dermatoscopic examination to determine biopsy indication [9].

The lesions that are considered to be malignant and develop at the level of the vulvar mucosa are described using ABCDE criteria. A-for asymmetry lesions, B-for irregular edges, C-for most often very dark color, sometimes with more colors, among which can be found shades of red or blue, D-for a diameter larger than 6mm and E-for lesions that evolve most often in a short time. A number of early signs may draw attention

to an atypical vulvar lesion on a possibly malignant substrate, such as changing the size of the lesion, its shape or color. Itching at that level may be an early symptom as well. A number of signs, but also symptoms, may be more specific for a vulvar malignant lesion, but they usually appear much too late in the tumor evolution, when the prognosis worsens considerably, among these signs and symptoms are listed, ulceration, bleeding or pain [10].

A subtype of vulvar malignant melanomas, especially those that come from the outer portions, without hairs of the large labia, may have as etiopathogenesis the same risk factors as the cutaneous malignant melanomas. Also, several cases of vulvar melanoma have been described that evolved near a vulvar melanocytic nevus [11]. Other risk factors implicated in the etiopathogenesis of malignant melanomas are viral infections, chronic inflammatory diseases, irritant chemicals and genetic factors [12].

Symptoms described by patients with vulvar melanoma include bleeding, itching, vaginal discharge, dyspareunia or a palpable / visible tumor formation [13]-[18]. An optimal investigation plan for a patient with vulvar melanoma should include a thorough examination of the genital and pelvic regions, with biopsy sampling (punch-biopsy or biopsy-excision if the anatomy of the lesion allows it) to establish the diagnosis of certainty, followed by a computer-tomographic examination of the pelvic region or have an MRI examination of the same region, and finally examination with the help of a CT or PET-CT examination of the other regions to investigate possible metastases [19]. As a staging of this neoplasm, the classic staging of malignant melanoma (TNM) is used. According to a prospective clinico-pathological study performed by the Gynecological-Oncological Group on primary vulvar melanoma, which evaluated international staging systems, it was concluded that the most efficient staging system regarding the long-term survival of patients diagnosed with vulvar melanoma without recurrence. has been AJCC since 1922 [20]-[25]. The prognosis depends on the stage of the disease, and the survival at 5 years from the diagnosis of the patients with vulvar cancer, varies between 77% in stage I and 24% in stage IV of the disease [8].

Regardless of the surgical approach of a vulgar melanoma, a large majority of patients will develop into metastases. Therefore, the therapeutic approach of a disease is not necessary to prevent patients and the quality of life for a boy or patient for metastasis care is expected.

In patients diagnosed with vulvar melanoma without distant dissemination, the technique of local excision with wide margins instead of pelvic exenteration was adopted. For the control of the disease, radical vulvectomy is reserved for adults only. Thus, surgical management includes local excision with 1 cm margins for melanomas with thickness index <1 mm, and if anatomical localization allows, the resection margins should be extended to 2cm for tumors with thickness >1 mm [26]. The surgical technique includes excision of all layers up to the muscle fascia [27]. Studies in several countries have established a significant morbidity associated with more radical surgical procedures [28], [29]. Although more radical surgical procedures have shown local control of the disease than limited surgical procedures, the later metastases in most cases suppress the benefits of these aggressive procedures [30]-[32]. Thus, a series of retrospective data available until the present have shown that a more conservative surgical approach does not influence long- and medium-term survival [33]-[35].

The next step after primary excision is evaluation of sentinel lymph nodes in patients with vulvar malignant melanoma, which is practiced in most cases, but whose efficacy is uncertain [36], [37]. The thickness of the tumor together with the positive lymph nodes for malignant infiltration analyzes in a recent study performed by the Gynecological Oncology Group establishes the technique of elective regional lymphadenectomy, but only in the prognosis affects. However, in small series a benefit is established regarding the survival of the patient's care and the beneficiary of the elective regional lymphadenectomy technique [23], [38].

A number of recent studies have also shown that a radical vulvectomy associated with bilateral lymphadenectomy of the inguinal femoral lymph nodes does not offer long-term survival advantages compared to the surgical approach to melanocytic malignant vulvar tumor [39]-[40].

The efficacy of adjuvant therapies that can be used in patients with vulvar melanoma is limited to this date. These include Interferon alfa-2b, Temozolomide chemotherapy, cisplatin, etc., or Nivolumab immunotherapy [41]. An important step in establishing the optimal therapeutic behavior is to establish whether or not the BRAF gene (10% of patients with mucosal melanoma) or the somatic KIT mutation (25% of the patients with mucosal melanoma) are to verify the possibility of targeted therapy initiation [42], [43].

A number of experimental studies have shown an increased toxicity and low tolerability of perilesional tissues, being recommended only in the multifocal presentation of vulvar melanoma due to the difficulty of complete resection [44].

Topical treatment with Imiquimod has been used in several experimental studies for the treatment of lentigo malignant and cutaneous metastases from malignant melanoma, so it was used in the case of three patients with recurrent vulvar melanoma, which leads to local control of the recurrences, but at a distance from several years, metastases were evident in all these cases [45]-[49].

The prognosis of long-term disease is low, any therapy is chosen in the management of vulvar melanoma [50].

CONCLUSIONS

Vulvar melanoma is a rare disease commonly encountered in medical practice but it is one of the most common non-squamocellular malignant histopathological diagnoses described at vulvar level. The lesions that are considered to be malignant and develop at the level of the vulvar mucosa are described using ABCDE criteria, and a number of early signs may draw attention to an atypical vulvar lesion on a possibly malignant substrate, such as changing the size of the lesion, its shape or color. An optimal investigation plan for a patient with vulvar melanoma should include a thorough examination of the genital and pelvic regions, with biopsy sampling (punch-biopsy or biopsy-excision if the anatomy of the lesion allows it) to establish the diagnosis of certainty, followed by a computer-tomographic examination of the pelvic region or have an MRI examination of the same region, and finally examination with the help of a CT or PET-CT examination of the other regions to investigate possible metastases. In patients diagnosed with vulvar melanoma without distant dissemination, the technique of local excision with wide margins instead of pelvic exenteration was adopted. The efficacy of adjuvant therapies that can be used in patients with vulvar melanoma is limited to this date. These include Interferon alfa-2b, Temozolomide chemotherapy, cisplatin, etc., or Nivolumab immunotherapy.

The prognosis of long-term disease is low, any therapy is chosen in the management of vulvar melanoma.

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