Case Reports

Management of vulvar melanoma and review of the literature

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Summary

Background: Vulvar melanoma represents a rare group of malignancies and is the second most common vulvar malignancy. Treatment options range from local excision of the tumor and sentinel lymph node dissection to radical resection involving en bloc vulvectomy and inguinofemoral lymphanedectomy. Vulvar melanomas have an overall poor prognosis, and there is lack of consensus in the published literature regarding treatment options. *Objective:* To discuss the management of vulvar melanomas through review of the actual literature. *Methods:* Identification of studies through computerized searches (January 2006) was conducted using MEDLINE (1966 to present), the Cochrane Central Register of Controlled Trials, the National Research Register and the Medical Research Council's Clinical Trials Register. The medical subject headings and text words used were: vulvar melanoma, malignant, management, case report, and therapy. The literature review was done over the past 36 years. *Result:* Results of these primary retrospective series have shown no improvement in the overall recovery or disease survival rates. *Conclusion:* Patients with malignant melanoma are often diagnosed at 70 years of age with multiple comorbidities. Less radical surgery presents a more realistic option for many patients without decreasing their survival rates. Surgery is still the gold standard of treatment and offers the best available treatment for controlling and potential curing of malignant melanomas. However, the whole concept of therapy should be tailored to meet the specific needs of individual patients.

Key words: Malignancy; Melanoma; Vulvar.

Introduction

Vulvar melanoma is the second most common vulvar malignancy, with an incidence of 0.26 to 0.52 cases per million [1], arising within the vulva and accounting for 8-10% of all vulvar malignancies [2]. It occurs predominantly in postmenopausal women and the median age at diagnosis is 70 years [1]. Malignant melanomas occur preferentially in the vulvar skin. Most of these melanomas arise de novo, but may also arise from a pre-existing junctional nevus. It has been suggested that ultraviolet light may be etiologically involved indirectly by causing cell-mediated systemic alteration of immune responses [1]. However, contrasting time trends of skin or vulvar melanoma suggest that pathogenesis of vulvar menaloma is less dependent on DNA damage induced by ultraviolet light [1]. Most patients remain asymptomatic except for pigmented lesions. There are three histologic types of vulvar melanoma, namely, mucosal lentiginous melanoma, superficial spreading melanoma, and nodular melanoma. The International Federation of Gynecology and Obstetrics (FIGO) staging for squamous lesions is not applicable to these melanomas and the 5-year survival rate is poor, ranging from 27-54%, and often related to the depth of tumor invasion rather than to the diameter of the lesions. There are still controversies regarding the treatment of the disease [2]. We therefore decided to review the actual literature systematically over the past 36 years and also present here a case of a 75-year-old woman with malignant vulvar melanoma with a Breslow depth of 4.5 mm.

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Case

A 75-year-old woman was initially referred by her gynecologist to the Department of Gynecology at the University of Giessen, Germany with a vulvar lesion. She had experienced a burning feeling in the vulvar area the previous couple of months. Physical and gynecological examination showed massive involvement of the vagina and suburethral area. Primary tumor was localized at the left labia majora (Figure 1). A punch biopsy was performed and specimen sent for pathological examination.

Histologically a malignant spindle-cell and pleomorphic tumor was found infiltrating the subepithelial connective tissue. About 30% of the tumor cells contained a brown pigment which was also found in the cytoplasm of interspersed macrophages. Immunohistochemistry showed that the tumor cells were positive for vimentin, S-100 protein, HMB-45, and Melan-A. Cytokeratin was negative. These findings indicated a pigmented malignant melanoma of the vulva. To exclude distant metastasis, a computed tomography (CT) scan of the abdomen and chest, and a magnetic resonance imaging (MRI) scan of the head were performed. Neither radiological examination showed any signs of metastasis. An unspecific tumor marker (S100) for melanoma was taken and showed normal levels (0.10 µg/l, cutoff margin: 0.10 µg/l).

The patient had multiple comorbidities (diabetes mellitus, chronic coronary disease, essential hypertension and was overweight) with two histories of ischemic stroke. She was on a lifelong marcumar treatment but had no previous history of gyne-

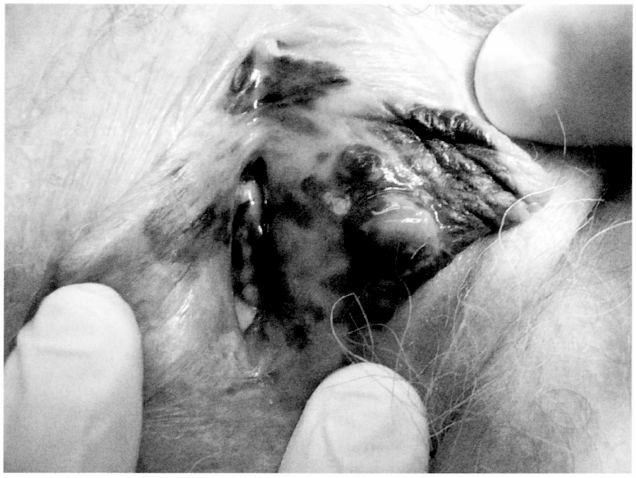

Figure 1. — Diffuse vulvar malignant melanoma.

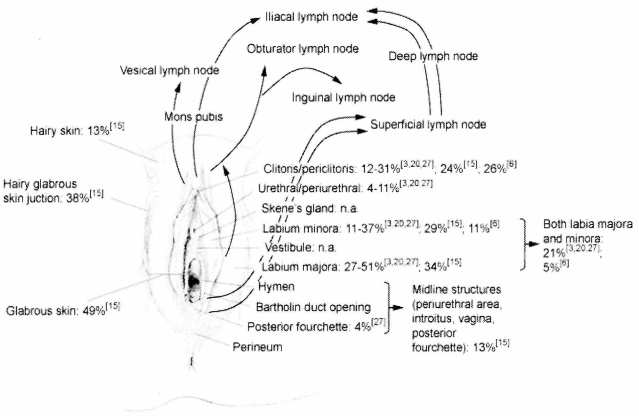

Figure 2. — Location of vulvar melanoma (with references cited); n.a.: not available.

cological surgery. Due to urethral orifice involvement, preoperative planning was undertaken with a urologist to achieve complete excision of the melanomas. A complete hysterectomy, salpingo-oophorectomy, colpectomy, and radical vulvectomy with total resection of the urethra were performed as curative treatment. The operation was limited only to removal of the primary tumor because of the high morbidity of the patient (diabetes mellitus and history of ischemic stroke). Wound healing was achieved in 14 days after the operation.

In the final histopathological report, malignant melanoma was confirmed showing extension to the lymphatic vessels and small veins. The tumor thickness according to Breslow was 4.5 mm, equivalent to a Clark level IV. Complete excision of the lesion was completely achieved (R0). The disease was staged as pT4b, L1, V1, R0.

Thereafter, the patient was discharged from the hospital with primary wound healing. No adjuvant therapy was planned and a three-monthly follow-up was arranged. After nine months of follow-up, there is no clinical sign of recurrence but the patient remains on a three-monthly observation program.

Discussion

At least two good reasons compel us to present this case of a primary melanoma of the vulva and discuss the therapy. Thus, although rare in absolute numbers (0.1 to 0.15 per 100,000 females in population-based studies [3, 4]), these tumors are rarely expanded and extended from the labia majora to the paraurethral area and vaginal introitus (Figure 1). Vulvar melanoma was first reported as primary vulvar melanoma in Lancet in 1861 by Prescott Hewett [5] at St. George's Hospital in London under the title "Melanosis of the labium and glands of the groin and pubes".

Vulvar melanoma represents less than 1% of all melanomas, yet it is the second most common vulvar malignancy after squamous cell carcinoma and mostly found in advanced age, with an average age at presentation of 66 years [6]. The disease has also been reported in adolescents and teenagers [6] where an incidence of 0.108 per 100,000 persons was reported [3]. Figure 2 shows the anatomic location of vulvar melanoma [7]. The most common location of primary vulvar melanoma is the labia majora followed by the labia minora.

According to Wechter *et al.*, the average time between onset of signs and symptoms to presentation for medical care is approximately four months [6]. This finding is similar to our case report, where the patient had felt the symptoms for a couple of months, but ignored them at the beginning.

Table 1 presents the commonly observed symptoms of malignant melanoma. In all these cases the most common symptoms were pruritus, lumps, tumor mass, swelling, or abscess.

Genetic and environmental factors contribute to pathogenesis of cutaneous melanoma, and it is likely that diverse risk factors may be identified for vulvar melanoma as well. Familial history and genetic susceptibility alleles are likely to be important risk factors although there is relatively limited data to support this thesis. Wechter *et al.* [6] reported that 15% of their 20

Table 1. — *Symptoms of malignant melanomas.*

Symptoms	Reported frequencies	
	Wechter *et al.* [6]	Other authors [3, 8, 9, 10]
Bleeding	17%	17-42%
Mass, lump, swelling	23%	28-72%
Discharge	0%	20%
Pruritus	23%	2-19%
Pain	7%	7%
Lesions found at routine examination	15%	n.a.
Lesion noted visually by patient	17%	n.a.
Dysuria	7%	n.a.
Nonhealing sore, spotting	3%	n.a.
Alteration of urine stream	3%	n.a.
Foul odor	0%	n.a.
Weight loss	not mentioned	reported without defined frequency [3]

* Numbers in brackets correspond to references.

Table 2. — *Staging system for melanomas.*

Stage	Clark	Chung	Breslow	AJCC [11]	FIGO [2]
I	Intra-epithelial	Intra-epithelial	< 0.76 mm	pT1, N0, M0 Primary melanoma < 0.75 mm thick and/or Clark's level II pT2, N0, M0 Primary melanoma 0.76-1.50 mm thick and/or Clark's level III	Tumor confined to vulva or vulva and perineum, 2 cm or less in dimension
II	Into papillary dermis	< 1 mm from granular layer	0.76-1.5 mm superficial invasion	pT3, N0, M0 Primary melanoma > 1.51-4.00 mm thick and/or Clark's level IV. No nodal or systemic metastasis	Tumor confined to the vulva or vulva and perineum, 2 cm or more in dimension
III	Filling dermal papillae	1.1-2.0 mm from granular layer	1.51-2.25 mm intermediate invasion	pT4, N0, M0 Primary melanoma > 4.0 mm thick and/or Clark's level V and/or satellite(s) within 2 cm of the primary tumor. No nodal or systemic metastasis Any pT, N1, M0 Regional nodal metastasis ≤ 3 cm in dimension. No systemic metastasis Any pT, N2, M0 Regional nodal metastasis > 3 cm in dimension or intransit metastasis. No systemic metastasis	
IV	Into reticular dermis	> 2 mm from granular layer	2.26-3.0 mm intermediate invasion	Any pT, N, or M1 systemic metastasis	Tumor invades bladder mucosa, rectal mucosa, or upper urethral mucosa, or is limited to bone or distant metastasis including pelvic lymph nodes
V	Into subcutaneous fat	Into subcutaneous fat	> 3 mm deep invasion		

* Modified from Novak's Gynecology [13].

cases of vulvar melanoma had a familial history of melanoma in a blood relative, equivalent to that reported for cutaneous melanoma. Although ultraviolet light exposure may be a primary environmental predisposing factor, a germline mutation in melanocortin type 1 receptor R151C polymorphism has also been suggested to be a risk factor for cutaneous melanoma [8-10], but not for vulvar melanoma [6]. This certainly does not appear in vulvar melanoma since the vulva location is inaccessible to direct light exposure.

Pathological findings

Tumor cells are derived from melanocytes arising from neural crest cells located in the basal layer of the epidermis. These malignant tumors of neuroectodermal origin arise from junctional nevi, compound nevi, or de novo from epidermal melanocytes in the basal layer of squamous epithelium. Pathologically they were classified as superficially spreading melanomas, nodular melanomas, and mucosal lentiginous melanomas.

Staging

The FIGO staging used for squamous lesions is not applicable to melanomas because the lesions are usually smaller and the prognosis is related to the depth of tumor invasion rather than to the diameter of the lesion. The most commonly used staging systems were established by Clark, Breslow and modified by Chung (Table 2). However, most authors currently prefer the four-stage system suggested by the American Joint Committee on Cancer (AJCC) [11] as revised in 2001 [12]. Table 2 presents a summary of the staging systems for melanomas.

Surgical management

Since vulvar melanomas have an overall poor prognosis, there is lack of consensus in the published literature regarding treatment options. However, surgery has been and still is the gold standard of the treatments.

In the 11 largest studies of surgical strategies, none offered a significant survival advantage [14, 15]. Retrospective studies suggest that radical vulvectomy does not improve survival rates over the more limited resection for vulvar melanomas. However, when primary melanomas of the vagina or vulva spread to the urethra or rectum, it may be necessary to perform an anterior (extirpation of the vaginal wall, the uterus, the adnexa and the bladder, but leaving the rectum) or posterior (removal of the uterus, the posterior vaginal wall and the rectum) exenteration, whereas additional hysterectomy has been rec-

Table 3. — *Surgical management as reported in different studies.*

Reference	Number of patients	Survival
Rose *et al.* [19], 1988	26(12 CS/14 RS)	NS
Bradgate *et al.* [20], 1990	50 (21 CS/23 RS)	NS
Trimble *et al.* [21], 1992	80 (18 CS/59 RS)	NS
Tasseron *et al.* [22], 1992	30 (8 CS/18 RS)	NS
Trimble [23], 1996		NS
Raeber *et al.* [24], 1996	89 (22 CS/47 RS)	NS
Scherstroen *et al.* [25], 1995	65 (17 CS/48 RS)	NS
DeMatos *et al.* [26], 1998	30 (19 CS/11 RS)	NS
Ragnarsson-Olding *et al.* [27], 1999	123 (35 CS/63 RS)	NS
Verschraegen *et al.* [28], 2001	51 (31 CS/14 RS)	NS

CS: Conservative surgery (Local excision, hemivulvectomy); RS: Radical surgery (radical vulvectomy, partial vulvectomy); NS: not significant.

ommended when the melanoma is in the upper third of the vagina [16]. Table 3 provides a summary of these reports. Primary localized vulvar melanoma is adequately treated by local excision with adequate and histologic tumor-free margins. Irvin *et al.* [2] concluded that 1-cm skin margins are adequate for vulvar melanomas < 1 mm thick, and that 2-cm margins are adequate for intermediate-thickness melanomas (1-4 mm). Regardless of the thickness of the lesions, in all cases it is necessary to include at least a 1-cm deep margin extending through the subcutaneous fat to the muscular fascia below [2]. Since thick melanomas (larger than 4.0 mm) are associated with a high risk of nodal and distant metastases, more extensive resection is not likely to improve the outcome substantially [17]. According to Heaton *et al.* [18], there is no significant benefit with respect to either local recurrence or overall survival rates among patients with thick tumors who underwent excision with margins greater than 2-cm. Thus, a 2-cm margin is probably adequate [17].

A biopsy from the left primary tumor was performed and histology revealed malignant melanoma. Staging examination including MRI of the head and abdominal CT showed no distant metastasis and no lymphadenopathy. Before the surgical intervention, the case was discussed in a routine multidiscipline oncological conference regarding the question of therapy. The treatment of choice was surgery. With extension of the melanoma from the left labia to the urethra orificum and vaginal wall (Figure 1), complete excision of the female genital organ was performed to achieve wide, tumor-free surgical margins. Pathological examination showed that a R0 status was reached including the urethral orificum area. The patient was free of disease at the 9-month follow-up.

Role of elective lymphadenectomy

There are controversies regarding the advantages of elective (prophylactic) lymph node dissection in vulvar melanoma with respect to tumor recurrence and/or patient survival [15]. Usually inguinofemoral lymphadenectomy is not done for early lesions that are < 0.76 mm thick and have no evidence of lymph vascular space invasion. The two traditional variations of lymph node dissections, elective and therapeutic, have today extended to a third variant, the 'selective lymph node dissection' with radionuclide markers (eg. ^{99m}Tc-labeled sulfur colloid) or blue dyes (isosulfan blue, patent blue, methylene blue), the so called 'sentinel node'. With the hypothesis that melanoma cells spread to regional nodal basins before metastasizing widely (incidence of 50% [15] for distant metastases in patients with microscopically negative lymph nodes), debate over the merits of elective lymph node dissection has largely been subsumed by the sentinel lymph node biopsy [17]. Regional disease was also detected in 30% [14] of patients with urogenital melanomas during initial staging. For melanomas more than 1 mm thick, sentinel lymph node staging can be considered in order to estimate the prognosis and to determine eligibility for clinical trials, and the need for adjuvant therapy [17]. Pelvic lymph nodes are most often involved [14]. In a Swedish study, overall 5-year survival was 26.8% for node positive, and 65.2% for node negative vulvar melanomas [27].

Melanomas located in the clitoris area metastasize mostly to pelvic nodes through lymph vessels lateral to the symphysis (Figure 2). Radical inguinofemoral lymphadenectomy at the time of primary surgery may be performed only in cases of clinically positive lymph nodes [16]. A local control of tumor was important in our patient. Through in advanced age, adipose of the patient and diabetes mellitus, removal of the lymph nodes is considered as additional morbidity for patients in terms of longer surgical time, groin incision for the inguinal lymphadenectomy and risk of lymph edema. Since palpation and radiological examination showed no lymphanedopathy in the inguinal area, neither lymphatic sampling nor prophylactic lymphadenectomy was done. Although a sentinel lymph node biopsy has been a feasible, low morbidity operation, those studies were still insufficient to demonstrate the survival advantages, outcome, accuracy, and associated morbidity [14]. Further investigations with longer follow-up and in multicenter studies are needed.

Survival and prognostic indicators

A number of variables have prognostic value, including the patient's age, anatomical location of the primary tumor, size, Clark's level, Breslow's thickness, and histopathologic type. Diameter of tumor, age at diagnosis, family history and adjuvant therapy are other possible prognostic factors in addition to the prognostic factors for vulvar melanomas. Ulcerations have become a significant determinant of disease-free or long-term survival because they are associated with a biologically more aggressive lesion and a poorer prognosis. Balch *et al.* [29] reported that the survival rate dropped from 80% for non-ulcerated melanomas to 55% for ulcerated melanomas.

Tumor invasion into capillaries and central localization of the tumor in the vulva have emerged as independent variables for vulvar melanomas [15]. Macroscopic amelanosis tends to be aggressive and denote a poor prognosis [15].

The overall survival of patients with vulvar melanoma is poor and the average 5-year survival rate ranges from 27% to 60% as calculated by individual investigators [2, 6, 15].

Surveillance aimed at early detection of new lesions is needed. However, routine laboratory tests, including serum lactate dehydrogenase, albumin, and plasma hemoglobin measurements and chest radiography have not been shown to be beneficial in screening for visceral disease in asymptomatic patients [17]. Finally the prognostic factors could be improved with early detection of melanomas. Yet patient or physician delay in diagnosis has not been confirmed.

Adjuvant therapy

Malignant melanoma is generally considered to be a radioresistant tumor [2]. However radiotherapy may be

useful for controlling symptoms in advanced-stage disease, although its use in routine and palliative management has never resulted in cure [2]. Chemotherapy has also been found to be ineffective. So far, Dacarbazine (DTIC) is the only active chemotherapeutic agent to date, with response rates ranging from 15 to 25%. The efficacy of adjuvant interferon α2b therapy has been tested in clinical studies and vaccine alternatives to high-dose interferon α2b therapy have gained interest in melanoma therapy. Interleukin-2 has been accepted as a standard treatment of metastatic melanoma alone or in combination with chemotherapy [2].

In conclusion, many patients with malignant melanoma are often diagnosed at about 70 years of age. They often have multiple comorbidities including wound healing difficulties. In the face of these challenges, less radical surgery presents a more realistic option for many patients without decreasing their survival rates. Also, elective node dissection seems to offer no additional advantage in superficial lesions (< 0.76 mm in thickness), and its role in deeper lesions is still unclear. At present, surgery is still the gold standard of treatment and offers the best available treatment for control and potential cure of malignant melanomas. However, the whole concept of therapy should be tailored to reflect the condition, social status, and specific needs of the individual patients.

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