Vulvar melanoma with urethral invasion and bladder metastases – a case report and review of the literature

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Vulvar melanoma is an aggressive neoplasm with a poor prognosis. Approximately 25% to 50% of patients survive 5 years [1]. This malignancy is prone to late metastasis, so 5-year survival does not equal cure. The management of recurrent disease continues to be experimental and individualized [2].

We present a case of metastatic vulvar melanoma, treated with local re-excision and chemotherapy, with a long survival time of 51 months.

In September 2008, a 59-year-old woman was admitted to the Department of Gynecology and Obstetrics of one of the Wielkopolska Region hospitals, due to a palpable vulvar mass in the urethral area. Her medical history revealed hypothyroidism. There was no significant family history, and no other abnormalities were detected by physical examination. A tumor (polyp) was clinically diagnosed. The patient was initially treated with local excision of the lesion, without tumor-free surgical margins. The histopathology revealed carcinomatous infiltration of the caruncle, covered with a thinned stratified squamous epithelium. Several possible diagnoses were suggested, including squamous cell carcinoma, malignant melanoma and urothelial carcinoma. The histological diagnosis was confirmed by positive immunostaining with monoclonal antibody to human melanoma (HMB-45+). Immunohistochemistry also showed vimentin and S-100 positive staining, cytokeratine clone AE1/AE3 positive staining in about 30% of the cells, Ki67 positive in more than 47% of the cell nuclei. The final histopathologic report confirmed the diagnosis of malignant melanoma.

In October 2008, the patient was referred to the Department of Gynecological Oncology, Clinical Hospital of Gynecology and Obstetrics, Poznan, in order to undergo a radical vulvectomy. Physical examination revealed an area after local excision of the lesion from the vaginal vestibule, 0.5 cm from the urethra. A total vulvectomy was performed, together with inguinal lymph node dissection. The histopathologic diagnosis revealed multifocal malignant melanoma of the vulva, confirmed by positive immunostaining with monoclonal mouse antibody against melanoma antigen Clone PLN2, S-100 and vimentin (Figures 1–4). A multifocal neoplastic lesion on the whole vulvar area was described (a lesion extending to the incision line from the side of the vagina). An infiltration to the dermis, not exceeding the depth of 1 mm, was noted (the place of
the deepest infiltration was diagnosed in the area of the previously extracted focus. A neoplastic focus was found in one lymph node on the left side. Owing to the lymph node metastases, the patient was considered to be at high risk of recurrence and received postoperative adjuvant therapy with dacarbazine – 6 cycles.

In December 2010, approximately 21 months after the first-line treatment, the patient was readmitted due to a hemorrhagic nodule lesion in the vaginal vestibule and was treated with local excision. A wide neoplastic multifocal lesion was detected. The histological report showed a malignant melanoma. Immunohistochemistry showed melanoma, S-100 and positive staining for vimentin. Again the patient received four cycles of chemotherapy with dacarbazine.

In January 2013, the patient was readmitted to the department for further treatment. In examination there were four solid nodules in the area of the urethra and vaginal vestibule, hemorrhagic and painful on physical examination. The ultrasound examination revealed an irregular lesion in the bladder (4 cm × 5 cm in size). After a month, another two hemorrhagic nodules (7 and 5 mm in diameter, respectively) were found over the urethra (Figure 5). Due to invasion of the urinary tract the patient was referred to a urologist, but the consultation disqualified her from surgery.

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In general, little is known about the pathogenesis and risk factors of vulvar melanomas. While sun exposure is a well-established etiological factor for cutaneous malignant melanomas, it is unlikely to be implicated in vulvar melanomas because of their localization on the sun-shielded parts of the body. In a study among Caucasians in Sweden, East Germany, the USA and Victoria (Australia), conducted to determine the influence of sun exposure on the incidence of vulvar melanoma, opposite latitudinal trends were observed: vulvar melanoma incidence rates increase from south to north, while those of cutaneous malignant melanoma on sun-exposed skin areas decrease from south to north [14]. This confirms the assumption that solar UV radiation not only cannot be considered a risk factor for vulvar melanomas but it even seems to have a protective effect against this malignancy, possibly due to its role in vitamin D photosynthesis in the exposed skin [14]. The study also revealed that whereas a rising trend of incidence for cutaneous malignant melanoma was observed until recently, the incidence of vulvar melanoma has either decreased or remained constant [14]. Histologically, the order of the incidence of each subtype was also reverse to that observed in cutaneous melanomas [11]. Therefore, it is clear that vulvar melanoma should be investigated separately from cutaneous melanoma.

Among other possible risk factors, viral infections such as human papilloma viruses, human herpes viruses, and polyomavirus were considered, but their role in the etiopathogenesis of mucosal melanomas was not confirmed [15–17].

Malignant melanoma spreads in three different ways: by giving metastases to regional lymph nodes, by direct distant metastases, and by satellite or in-transit metastases [18]. In vulvar melanoma, metastases are most commonly found in the inguinal lymphatic nodes (Table I). Other reported metastatic sites are the lungs, vagina, liver and brain [13, 19]. In the case of our patient, the metastases were found in the urethra and in the bladder, both of which are very unusual metastatic areas for vulvar melanoma.

Most of the lesions are unifocal, although Kerley et al. reported a multifocal malignant melanoma arising in vesicovaginal melanosis [20], and Podczaski et al. reported a case of multiple cutaneous and vulvar melanomas and a subsequent malignant melanoma of the cervix [21]. In our case the diagnosis also indicated a multifocal malignant vulvar melanoma.

There are no well-established protocols for staging and treatment of mucosal melanomas due to their rarity. Most authors recommend applying standard operative staging and resection principles of cutaneous melanoma for vulvar melanoma patients [22, 23]. Historically, radical vulvectomy and bilateral inguinal lymphadenectomy were recommended for all patients, regardless of lesion size, thickness or depth of invasion [8, 24]. However, many recent investigations reported no significant differences in the overall survival rates between patients treated with radical compared to conservative surgery [11, 12, 22, 25–27].
Table I. Outcomes of larger group studies on patients with vulvar melanoma from the last decades

| Author   | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initial inguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors | Conclusions                                                                 |
|----------|--------------|--------------------|--------------------------------|----------------------------------------------------------|------------------------------------------|----------------------------|-----------------------|-----------------------------|-----------------------------|-------------------------------|-----------------|-----------------------------|-------------------|--------------------------------------------------------------------------------|
| Chung    | 44           | 54.5               | –                              | Lungs, liver, brain, myocardium, kidneys, adrenals, stomach, retroperitoneal nodes | Wide LE (7) Small LE (3) RV (28) SV (1) Primary RT (1) Exenterative procedure (1) No therapy (1) | Inguinal and pelvic node dissection (19) Inguinal node dissection (9) BGD (30) Biopsy (1) | RT CHT | –                          | –                            | –                            | 30.3             | 27.2                        | Depth of invasion | Minimal therapy recommended is radical vulvectomy with bilateral inguinal-femoral node dissection. 50% positive lymph nodes at presentation, 11% of which were clinically negative. Most common site of recurrence: groin (20.5%). |
| Ariel    | 45           | 56                 | –                              | Ovaries                                                   | RV                                        | BGD                          | RT                    | –                          | –                           | –                            | –                            | –                            | Presence of satellites, lymph node involvement, urethra and/or vagina involvement | Metastases in inguinal nodes in 32% at presentation – routine removal of these doubtful. No cures were obtained from RT |
| Podratz  | 48           | 60.2               | Vulvectomy (47)                 | Pelvic lymphadenectomy (23)                               |                                          |                              |                       | 54                            | 54                          | 54                            | 71%             | 38%                        | Histologic growth patterns, lymph node involvement, depth of invasion | 5-year survival rates: 71% for superficial spreading and 38% for nodular melanoma |
| Author | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initial inguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors | Conclusions |
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| Bradgate 1990 [26] | 50 | 63.7 | 7.45 | – | LE (18) RV (22) SV (2) HV (3) V (2) V + urethrectomy and vaginectomy (1) Biopsy only (2) | BGD (11) Pelvic nodes dissection (5) | RT (1) Palliative RT (10) CHT (5) – recurrent/disseminated disease | – | – | 23 | 35 | 22 | Clinical stage, patient age, tumor ulceration, cell type and mitotic rate | No significant relation between survival and type of surgery performed; tumor thickness was of prognostic importance but as a prognostic variable it did not operate independently of stage; 13% had metastases in lymph nodes histologically but not clinically |
| Trimble 1992 [48] | 80 | Wide LE (9 = 12%) HV (10 = 13%) RV (59 = 76%) | BGD/UGD (56 = 70%) | 193 | 63 | Breslow depth invasion, inguinal node metastasis, age at diagnosis | Breslow depth of invasion correlated with lymph node involvement. Radical vulvectomy did not seem to improve survival over less radical procedures. Patients who have more than a superficially invasive melanoma should also have inguinal lymph node dissection |
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|-----------------|--------------|--------------------|--------------------------------|----------------------------------------------------------|------------------------------------------|----------------------------|-------------------|-----------------------------|-----------------------------|---------------------------|---------------------|---------------------|----------------------|-------------|
| Phillips 1994 [49] | 71           | 60                 | –                              | Pelvis                                                   | HV (34 = 47.9%), RV (37 = 52.1%)          | BGD (35 = 49.3%)            | –                 | –                          | –                          | –                        | –                   | –                   | AJCC stage – the only independent prognostic factor, Breslow depth of invasion is an independent risk factor of recurrence | 49.3% recurrence rate. Correlated with groin node status were: capillary lymphatic space involvement, central primary tumor location (i.e., bilateral/clitoral/T3), tumor size, FIGO stage, Breslow depth of invasion |
| Scheistrøen 1995 [27] | 75           | 67                 | –                              | LE (17), V (48)                                          | Primary RT (6), No therapy (4)            | BGD (23) UGD (3)           | RT (5)            | CHT – Dacarbazine (3)       | 99                          | 11                        | –                   | 46                  | 37               | Inguinal lymph node metastases, angiolymphatic invasion, clitoris localization, multifocal tumors, age at diagnosis, DNA ploidy, ulceration | 67% recurrence rate. DNA ploidy is an independent prognostic factor. Radical surgery does not improve prognosis and is not recommended when the inguinal lymph nodes are clinically negative |
| Author | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initialinguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors | Conclusions |
|--------|--------------|--------------------|-------------------------------|-------------------------------------------------|-------------------------------------------|---------------------------|---------------------|-----------------------------|-----------------------------|-------------------------------|----------------------|---------------------|----------------|-------------|
| Räber 1996 [23] | 89 | 59.4 | 3.76 | LE (30 = 33.7%)<br> V (21 = 23.6%)<br> RV (36%)<br> RT only (1 = 1.1%) | BGD/UGD (45 = 50.5%)<br> RT of inguinal region (6 = 6.7%) | RT (14 = 15.7%) | 39.9 | – | – | 36.7 | – | Age, Breslow thickness of invasion, Clark’s level of invasion, lymph node involvement, anatomic site, postoperative stage | Surgery should be performed in accordance with the accepted standards for cutaneous melanoma. Neither LE nor RV + BGD was beneficial for patients with melanomas thicker than 1.5 mm. Median survival:<br> - Without lymph node involvement: 65 months,<br> - With lymph node involvement:<br>   - 21 months,<br>   - LE – 31 months,<br>   - V – 39 months,<br>   - RV – 41 months |
| Creasman 1999 [50] | 569 | 66 | – | LE (40.4%)<br> Debunking (25%)<br> Radical surgery (21%)<br> No surgery (9.2%)<br> Unknown (3.17%) | BGD (47%)<br> RT (6%)<br> CHT (5%) | – | – | – | 63 | – | Clark’s stage | Occurrence of positive lymph nodes correlates with Clark’s stage. For smaller lesions, wide local excision is recommended. The role of lymphadenectomy in advanced disease remains unanswered |
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| Author                        | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initial inguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors                                                                 | Conclusions                                                                 |
|-------------------------------|--------------|--------------------|-------------------------------|----------------------------------------------------------|------------------------------------------|-------------------------------|----------------|--------------------------------------|-----------------------------|---------------------------------|--------------------------|-----------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------|
| Ragnarsson-Olding 1999 [11]   | 198          | –                  | –                             | –                                                        | *118 stage I patients                   | BGD/UNG (36 = 30%)             | RT (20 = 17%) | –                                    | –                          | –                              | 47                       | –                          | Staging, tumor thickness. For stage I only: tumor thickness, ulceration, number of mitoses, macroscopic amelanosis, preexisting nevi, extent of tumor invasion (lateral labia majora), patient age | The mode of treatment was not significant                               |
| Ver-schraegen 2001[12]        | 51           | 54                 | 4.4                           | Distant metastases in 15 patients:                        | Wide LE (23) HV (6) RV (11)             | BGD (17) UGD (7)                | –              | > 5 years for 40 patients            | 11                         | 41                             | 27                       | –                          | For overall survival and disease-free survival: AJCC stage, Breslow thickness, Clark’s stage | 63% recurrence rate of which 72% locoregional. 91% 5-year survival for stage I and 31% for stages IIA and higher. 23% had lymph node involvement at presentation. Surgical techniques do not seem to alter the prognosis |
| Author     | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initial inguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors | Conclusions              |
|------------|--------------|--------------------|--------------------------------|----------------------------------------------------------|----------------------------------------|----------------------------|----------------------|-----------------------------|-------------------------------|-----------------------------|----------------|----------------|------------------------|---------------------------|
| Jahnke 2005 [19] | 7           | 48.4              | 7.7                            | Regional lymph nodes, liver, brain, lungs, breast       | Local excision, hemivulvectomy           | BGD (5)                          | Immuno-therapy only (2), immuno-chemotherapy (dacarbazine + INF-α) (3), radiation (1) | 48.4                         | –                           | –                           | –                           | –                           | –                           | 28% recurrence rate |
| Sugiyama 2007 [10] | 644         | 68                | –                              | Distant metastases in 28 (43%) patients                | Conservative surgery (171 = 26.6%), Radical surgery (164 = 25.5%), Unspecified (241 = 37.5%) | BGD/UGD (179 = 27.8%), No lymph- nodectomy (236 = 36.6%), Unknown (229 = 35.6%), Unknown (11 = 1.7%) | RT (33 = 5.1%), No RT (600 = 93.2%) | –                           | –                           | 61                           | –                           | Age, stage, and lymph node involvement | 5-year survival rates for: – localized disease – 75.5%, – regional disease – 38.7%, – distant disease – 22.1%, – women aged ≤ 68 years 72.0%, – women aged > 68 years 47.7%, – 0 positive lymph nodes – 68.3%, – 1 positive lymph nodes – 29%, – ≥ 2 positive lymph nodes – 19.5%, for localized disease, no significant difference in 5-year survival between conservative and radical surgery. Nodal/distant metastases in 86 (13.4%) patients at presentation |
| Author          | No. of cases | Median age [years] | Breslow depth of invasion [mm] | Metastasis sites reported other than regional lymph nodes | Initial surgical treatment (no. of cases) | Initial inguinal treatment | Adjuvant therapy | Median follow-up time [months] | Disease-free survival [months] | Median time of survival [months] | 5-year survival rate (%) | 10-year survival rate (%) | Prognostic factors | Conclusions                                                                 |
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| Baiocchi 2010 [13] | 11           | 64.8               | 3.08                          | Bones, lungs, vagina                                     | Vulvectomy (11) + distal urethrectomy and colpectomy (1) | Uni-/bilateral inguinal lymphadenectomy (6) | CHT (fo	{\text{t}}emustine and dacarbazine) IM (interferon) (1) | 56.2                       | 15                             | 29.3                             | –                   | –                        | Lymph node involvement | Prolonged survival was only achieved in patients with no lymph node involvement |
| Moxley 2011 [22] | 77           | 62                 | –                             | Wide LE (24)                                              | BGD (41 = 52%)                        | RT (4)                                   | CHT (9)                          | –                           | –                             | –                               | –                   | –                        | Only the 2002 modified AJCC stage correlates with the overall survival. Breslow thickness is significant for recurrence but not survival | Surgical radicality did not influence recurrence rates or survival. AJCC-2002 staging system for cutaneous malignant melanoma applicable to primary vulvar melanoma. Standard operative staging and resection principles in cutaneous melanoma should be used for all vulvar melanoma patients |

LE – Local excision, RV – radical vulvectomy, SV – simple vulvectomy, HV – hemi-vulvectomy, V – vulvectomy unspecified, BGD – bilateral groin dissection, UGD – unilateral groin dissection, RT – radiotherapy, CHT – chemotherapy, IM – immunotherapy.
frequent distant recurrence rate should also be considered before applying aggressive surgical interventions associated with significant morbidity [28]. According to Irvin et al., for vulvar melanomas < 1 mm thick adequate skin margins are 1 cm, and for melanomas 1–4 mm thick they are 2 cm. Moreover, they strongly advise including at least a 1-cm deep margin extending through the subcutaneous fat to the muscular fascia below in all cases. As far as the elective node dissection is concerned, it seems to offer no additional advantage in superficial lesions < 0.76 mm thick, and its role in deeper lesions is still uncertain [29]. In most cases, a wide excision with 2–3 cm margins may replace radical vulvectomy [13]. Metastases to the bladder would be an indication for a radical cystectomy, but tumor progression and lymph node involvement make the benefit from the operation doubtful [30].

The literature agrees on the important prognostic role of regional lymph node involvement [10, 13, 23, 25, 27]; therefore elective bilateral inguinal lymph node dissection remains the standard lymph node staging procedure, but it is unclear whether it has a therapeutic role or any impact on the overall survival [13]. Some authors question the role of sentinel lymph node biopsy and sentinel lymphadenectomy [28], whereas others claim that it is a feasible method and recommend it for patients in the absence of a clinically detected metastatic lymph node [13, 31]. In a 2006 study [32], the clinical value of intraoperative lymphatic mapping and tumor-positive sentinel lymphadenectomy (LM/SL) in early-stage melanoma was investigated in 431 patients. The results confirmed the prognostic significance of LM/SL (fewer recurrences were observed) for early-stage melanoma draining to the groin basin, and therefore the authors recommend it as a standard procedure for patients with early-stage melanoma of the lower extremities and trunk [32]. Because of the first non-optimal treatment, our patient was qualified for radical vulvectomy. Such extensive surgery allowed us to assess the invasion in the inguinal lymph node and to administer adjuvant chemotherapy. Owing to that, the patient achieved remission for almost 2 years.

The Breslow invasion depth has also been proved by many authors to be a significant prognostic factor [8, 11, 12, 23, 24], although some investigators claim no correlation with the survival rate, only a predictive role of recurrence rate [22] or of lymph node involvement [33]. Jahneke et al. concluded that patients with an invasion of 4 mm or more have a high risk of distant metastases that is unlikely to be reduced with the use of radical vulvectomy and bilateral inguinalfemoral lymphadenectomy [19]. As there are no effective adjuvant therapies, such prognostic indicators may be used to plan the extent of the surgical treatment.

Monochemotherapy with dacarbazine, as the most active chemotherapeutic agent, with a 15–25% response rate, or combined immunochemotherapy (dacarbazine + interferon-α), is used as adjuvant therapy [29], although no general recommendations currently exist. As for cutaneous malignant melanoma, several trials have been made to assess the potential beneficial role of interferon in the adjuvant therapy in high-risk and metastatic melanomas. In 2003, a meta-analysis by Wheatley et al. concluded that adjuvant interferon-alpha reduces the recurrence rates of high-risk melanoma, but the effect on the overall survival remains unclear [34]. Years later, in the European Organization for Research and Treatment of Cancer (EORTC) 18991 trial, PEG-interferon-α2b (PEG-IFN-α-2b) was proven to increase the recurrence-free survival, but not the overall survival [35]. Another meta-analysis by Petrella et al. confirmed those results for high-dose interferon and pegylated interferon [36].

Some promising results have been obtained in the treatment with paclitaxel and carboplatin in patients with un-resectable stage IV cutaneous melanoma [37] and metastatic cutaneous melanoma [38], although considerable toxicity of these therapeutic agents was observed. In another study, the combination of paclitaxel, carboplatin and bortezomib was demonstrated to have no clinical benefit in metastatic malignant melanoma, but the study included only 17 cases [39].

Radiotherapy was not proven to improve the overall survival, but it can reduce the local recurrence rate [28]. A study on patients with mucosal melanoma of the head and neck recommends postoperative radiotherapy to optimize local control [40].

The use of imiquimod cream offers a new treatment perspective. Sadownik and Crawford [41] and Smyth et al. [42] reported cases of a successful topical treatment with 5% imiquimod of vulvar melanoma recurrence, and Wong et al. confirmed its efficacy in the treatment of lentigo maligna [43].

The discovery of KIT and BRAF mutations and the development of targeted agents that inhibit these oncogenic pathways may lead to significant advances in the treatment of metastatic melanomas. In order to assess the prognosis of patients with mucosal melanomas specifically, no universal staging system exists. In everyday practice, the Clark’s tumor invasion level [44] and Breslow tumor thickness classification [45] for cutaneous melanoma are applied.

The scale that is generally confirmed to be the most predictive of the overall survival for vulvar
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Primary mucosal melanomas are rare tumors with a poor prognosis. In comparison with cutaneous (80.8%) and ocular melanomas (74.6%), vulvar melanomas have the lowest 5-year survival rate, which ranges from 31.6% to 63%, with an average of 44.6% (Table I). They are characterized by a high tendency for local and distant recurrence. The investigations performed on larger groups report recurrence rates of 63% [12] and 67% [27] (Table I). Lotem et al. attribute the increased local recurrence rate not to surgical failure but to the inherent abnormality of melanocytes [46].

Age, stage and lymph node involvement were found to be significant for survival in vulvar melanoma [10]. In patients with positive lymph nodes, the 5-year disease specific survival is 24%, compared with 68.3% for those with negative lymph nodes [10] (for specific data see Table I).

In conclusion, despite various new treatments, there is no evidence that survival has improved over the last 40 years. It is important to qualify patients properly for the initial surgery as suboptimal treatment may influence the time to recurrence. It should be emphasized that vulvar melanoma may metastasize to the urinary tract, so attention should be paid to that during follow-up examinations.

Conflict of interest

The authors declare no conflict of interest.

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