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Case Report Gynecology & Obstetrics

Mycosis fungoides of the vulva

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ABSTRACT

Mycosis fungoides (MF) is an indolent form of non-Hodgkin lymphoma and the most common type of primary cutaneous T-cell lymphoma. The overall incidence of MF is approximately 4 per 1 million. Involvement of the vulva by MF is extremely rare, with only seven reported cases in the literature. At the vulva, it is mainly a metastatic lesion and rarely a primary malignancy. We describe a case of vulvar MF and discuss the previous cases. The presentation can easily be confused with benign skin disorders. A vulvar lesion can reflect a systemic disease. When a patient consults for a vulvar lesion it is therefore important not only to look at the vulva but also to examine her in and ask general questions. In a patient with a vulvar mass and cutaneous lesions on other locations MF should be considered in the differential diagnosis.

Keywords: Cutaneous T-cell lymphoma; mycosis fungoides; non-Hodgkin lymphoma; vulva.

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Non-Hodgkin lymphoma (NHL) may involve the female genital tract, often as a manifestation of systemic disease [1]. Mycosis fungoides (MF) or Alibert-Bazin syndrome, is an indolent form of NHL and the dominant component of primary cutaneous T-cell lymphoma (CTCL) [2, 3].

The overall incidence of MF is rare with only four cases per million [4]. Vulva MF is exceptionally mentioned in the literature. It is difficult to diagnose the disease because it mimics several benign skin disorders. It is therefore likely that vulva MF is under diagnosed. Underreporting could also be present because biopsies are generally not taken at the vulva but rather at other easily accessible skin locations. A Medline search August 10th 2018, with the terms vulva and mycosis fungoides revealed that there were only seven published cases [2, 3, 5–7]. The present case study will describe an additional case together with a review of the previous published cases.

CASE REPORT

A 58-year old woman, G1P1, consulted the outpatient clinic with a 4-week history of itching and a painless nodule in the right labium majus. Previous antibiotic treatment did not affect. At that moment, she received treatment with gemcitabine (400 mg per week intravenously) for mycosis fungoides (MF). The MF was diagnosed five years earlier after three years of complaints. The patient also suffered from hypothyroidism and hypertension. Since, one year she was menopausal.

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Her previous treatments for MF included PUVA and UVB (discontinued due to intolerance), interferon (discontinued due to liver function failure), bexarotene (discontinued due to multiple side effects), methotrexate, carmustine (discontinued due to contact dermatitis), topical corticoids and adjuvant radiotherapy.

On clinical examination, there was a red, hard, but painless nodule (3 cm) in the right labium majus (Fig. 1A). Lateral from the enlarged labium there was also a demarcated, hypopigmented or white patch. This lesion was suggestive for hypopigmented MF. On her forearm she had a patch with erythema and mild scale (Fig. 1B). The vulva nodule was excised, and the pathological assay showed that there was a dermal infiltration of small-cell lymphocytes, positive for CD3 on an immunohistochemical assay, confirming the diagnosis of MF. The patient continued to receive gemcitabine. A CHOP-scheme (cyclophosphamide, doxorubicin, vincristine and prednisone) was initiated four months later. This caused neutropenic fever, for which hospitalization and antibiotics were needed. Despite the combined cytostatic treatment, new tumor lesions appeared. Total Skin Electron Beam (TSEB) was initiated two months later for a period of five weeks. Four months after TSEB she received a haploidentical stem cell transplantation. Unfortunately, this was complicated by a graft-versus-host disease, neutropenic fever and hemodynamic instability. The patient deceased 13 months after the diagnosis of vulva MF.

DISCUSSION

The vulva can be involved by lymphoma's mostly secondary and sometimes primarily [1]. MF is the most common cutaneous T-cell lymphoma. MF still has an unclear etiology. The mean age for patients at the time of MF diagnosis is between 40 and 60 years [4] and it is more common in men then in women (2:1 male: female ratio) [8, 9].

Although MF has a predilection for sun-protected areas (bathing trunk distribution), they are uncommon in the vulva region. Typical areas for MF are the chest, inner arms, lower trunk, groin and buttocks [7]. A literature search revealed that there were only seven published cases of vulva MF [2, 3, 5–7]. In Table 1, current case together with the published cases are shown. In only one case, MF was a primary malignancy [6], in all the other cases, it had to be considered as a manifestation of an advanced stage of MF. In one case, it looked like a primary but the past medical history suggested that the patient had MF already for eight years on her breast [3].

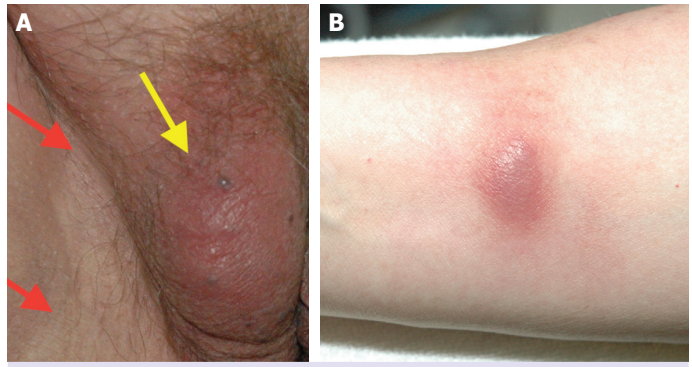

Figure 1. **(A)** Vulva MF: A dark red area and mass in the right labium majus (yellow arrow). Lateral from the labium, there is a hypopigmented lesion (red arrows). **(B)** Typical MF patch with erythema and mild scale on the forearm.

All cases of vulva MF were located on the labia. In five cases, there was a mass, in one case, only an enlargement of the right labia (x5), in one case, only pruritus and in one case of pruritus and a chronic fissure. In general, MF is characterized by progressive highly symptomatic skin lesions, including patches, plaques, tumors, and erythroderma [10]. Erythroderma, defined as >80% body surface involvement with patches and/or plaques, is associated with pruritus, leonine facies, skin atrophy, lichenification, and hyperkeratosis of the palms and soles [10]. The diagnosis of MF in general is difficult due to the non-specific skin lesions and the non-diagnostic biopsies. The patient with a chronic vulva fissure and MF, had in retrospect already MF on her breast eight years earlier [3]. It was only by assuming a possible clinical link between the two locations and repeating the biopsies that MF was diagnosed [3]. A delay in diagnosis or a misdiagnosis in MF is not uncommon. All women with a metastatic lesion at the vulva had skin lesions at other locations. Therefore, it is important to examine the patient detailed and ask her general questions when she consults for a vulvar dermatosis. When there are lesions at other locations and there is a possible clinical link one should take (new) biopsies at all locations. The differential diagnosis of MF lesions at the vulva are extensive and include very common infections, autoimmune diseases and rare malignant diseases (e.g., candida, herpes, intertrigo, eczema, lichen sclerosus, lichen planus, lichen simplex chronicus, psoriasis, Paget's disease, verrucous carcinoma, epithelioid sarcoma, myxoid leiomyosarcoma) [11–14].

The diagnostic algorithm for early MF is based on clinical, histopathologic, molecular/biologic and immunological criteria [15]. MF is staged according to

Table 1. Mycosis fungoides of the vulva

Author	Vang et al.	Reichman et al.	Buras et al.	Bakar et al.	Geller et al.	Geller et al.	Geller et al.	Tjalma et al.
Year published	2000	2010	2015	2015	2018	2018	2018	present
Age (years)	43	55	55	33	30	85	52	58
History MF (years)	2.5	8	none	7	10	5	3	5
Clinical presentation	no mass	no mass	right labia	mass (3 cm)	mass (2 cm)	mass (3 cm)	mass (U? cm)	mass (5 cm)
	pruritus	chronic	x 5	labium major	labium major	labium major	labium major	labium major
	dyspareunia	fissure	pruritus					pruritus
Accompanying skin lesion	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Treatment	CT	U?	Surgery	RT	mAb	RT	RT	CT
	Phototherapy	U?		Phototherapy	RT			RT
				IFN				stem cell transplantation
Status after vulva MF	AWD	U?	NED	NED	NED	DOID	AWD	DOID
F-U (years) after vulva	4	U?	13	1	U?	U?	U?	1
Involvement by MF								

U?: Unknown; IFN: Interferon; AWD: A live with disease; NED: No evidence of disease; DOID: Death of intercurrent disease; DOD: Death of disease.

the T (skin), N (lymph nodes), M (viscera) and B (blood) classification [16]. This TNMB classification stratifies patients into those with early-stage (stage IA to IIA) or advanced stage (stage IIB to IVB) disease [16, 17].

The treatment is based on the skin manifestations and the systemic disease. Patients with skin-limited disease respond well on skin directed therapies. Local therapy alone in these circumstances can produce remission and even cure. The local therapies can consist of topical chemotherapy (e.g., mechlorethamine or nitrogen mustard, carmustine), topical rexinoids (e.g., bexarotene), topical steroids, topical imiquimod, phototherapy [= Ultraviolet light, including UVB (wavelength 320–290 nm), narrow band UVB (wavelength 311 nm), and psoralen plus UVA (PUVA, wavelength 400–320 nm)] and radiotherapy (locally to a single lesion or group of lesions or to the entire skin surface via TSEBT (total skin electron beam therapy (TSEBT) [4, 10, 18]. Patients with extensive plaques and patches should receive intensive topical therapy to induce a complete remission followed by less intensive adjuvant topical therapy to sustain remission [10]. For patients with more advanced disease (tumors, erythroderma, nodal, visceral, or blood disease), curation is limited and the treatment should include cutaneous symptom palliation and systemic disease control [10]. Systemic therapy can consist of immunomodulator therapy (e.g., interferon), retinoids (e.g., isotretinoin, acitretin), rexinoids (e.g., bexarotene), denileukin diftitox, histone deacetylase (HDAC) inhibitors (e.g., vorinostat), extracorporeal photochemotherapy (ECP), systemic chemotherapy, allogeneic stem cell transplantation and emerging therapies (e.g., pralatrexate, cytokines, enhancer of T helper 1 cellular immunity (e.g., lenalidomide), proteosome inhibitor (e.g., bortezomib), purine nucleoside phosphorylase inhibitor (e.g., forodesine), in situ vaccination (intratumoral injection of a TLR9 agonist) combined with radiation and monoclonal antibody therapies (e.g., alemtuzumab, zanolimumab, brentuximab vedotin) [4, 10, 19, 20]. The participation of course in clinical trials, like always, should be stimulated.

The survival of MF depends on the stage. MF Patients limited patch and plaque (clinical stage IA) do not have an altered life expectancy and less than 10% will progress to more advanced stages [21]. The

median survival of MF patients with generalized patch and/or plaque (T2) is 11.7 years [22]. In this stage, 24% will experience disease progression to a more advanced clinical stage and approximately 20% eventually die of the disease [22]. In advanced MF (stage IIB to IV; tumors and erythroderma) the median OS is 63 months, with 2- and 5-year survival rates of 77% and 52%, respectively [17].

Except for one case, vulvar involvement of MF was a sign of disease progression and therefore associated with a poor prognosis. Partial and sometimes complete local remission could be achieved in these cases with local therapies. Radiotherapy for MF is in general very effective for early and advanced stage MF. Due to the tenderness of the vulva, it seems better to administer local radiotherapy in a low dose in multiple fractions (e.g., 4x2 Gy) instead of a single high dose of 8 Gy [2]. Exceptional is the case of primarily vulva MF with surgery as the sole treatment [6]. In this patient, the right labia minora et majora were five times the normal size. The skin was unremarkable for ulcerations, scaling plaques or microabscesses. She underwent a right hemivulvectomy with bilateral groin lymph node dissection. No adjuvant therapy was administered, and 13 years after the surgery, the patient is well with no evidence of recurrence [6].

Conclusion

Vulva MF is a diagnostic and therapeutic challenge. When confronted with a vulva dermatosis, a careful anamnesis and evaluation for a primary site elsewhere should be performed. The appearance can mimic benign skin diseases, and biopsies can be a false negative, causing a delayed diagnosis. It is important to repeat biopsies in case of the persistent lesion(s) with an unclear diagnosis. The approach seems aggressive, but it is the only way to reduce morbidity. Vulvar MF should be considered a sign of progressive disease with general a poor prognosis. The treatment should be tailored according to the symptoms and the extent of the disease. Local remission (partial or complete) can be achieved by local therapies.

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