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Successful treatment of primary non-Hodgkin's lymphoma of the vulva with radiation therapy

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Summary

Vulva, as a primary site of malignant lymphoma in women, is extremely rare. We report herein an 83-year-old patient with a primary, stage IIE vulvar, follicular center cell, B-cell lineage non-Hodgkin's lymphoma (NHL), with an excellent response to radiation therapy and event-free survival of 18 months. Early-stage primary vulvar NHL can be successfully treated only by limited field irradiation.

Key words: follicular center cell lymphoma, non-Hodgkin's lymphoma, radiation therapy, vulva

Introduction

The gynecologic tract is an uncommon primary site for NHL [1]. The genital tract lymphomas may be either localized or a part of systemic disease (most often secondary involvement). Vulva is a highly unusual site (4%) of primary involvement by lymphoma [1]. The first reported case of a primary NHL of the female genital tract was a vulvar case, described in 1937 by Taussig [2]. The most frequent histologic subtype is diffuse large B cell lymphoma [3-5]. A review of the literature reveals 2 reported cases of follicular center cell NHL primarily arising from the vulva with the B cell immunophenotyping [6,7]. We present herein the third case of primary follicular NHL arising in the vulva that achieved an excellent control with radiation therapy, and also review the relevant literature.

Case presentation

An 83-year-old woman consulted her physician with a painless swelling of the anterior third of the left labia majora, and a palpable mass of 4 cm. A biopsy taken showed atypical lymphoid infiltration. This was suspicious but inconclusive for malignancy. One year later the tumor grew to at least 10×10×15 cm and extended to the right labia majora, clitoris, and vagina and superiorly to the mons pubis. Also present on examination was moderate left leg swelling, bladder distention and enlarged right inguinal lymph nodes. The skin over the mass had multiple surface erosions. Incisional biopsy (2.5 cm in diameter) of the giant vulvar mass was performed. Histopathological examination revealed a lymphoid infiltration with follicular and diffuse pattern beneath the surface epithelium (Figure 1). Neoplastic follicles were closely packed and ill-defined, without marginal and mantle zones. The lymphoid infiltrate was composed of small to medium sized cells with angulated, cleaved nuclei, inconspicuous nucleoli and scant pale cytoplasm. There were also scattered large transformed cells, namely centroblasts, with vesicular nuclei and peripheral nucleoli. Immunohistochemically, CD20 (clone L26; Lab Vision, Fremont, CA, USA) staining showed follicular architecture by staining of the neoplastic B lymphocytes. CD3 (clone SP7; Lab Vision, Fremont, CA, USA) immunoreactivity was noted on the scattered reactive T cells inside the follicles and in the interfollicular area. Diffuse positivity of bcl-2 antibody (Lab Vision, Fremont, CA, USA) was also remarkable in the lymphoid infiltrate. CD23 (clone SP23; Lab Vision, Fremont, CA, USA) demonstrated increased

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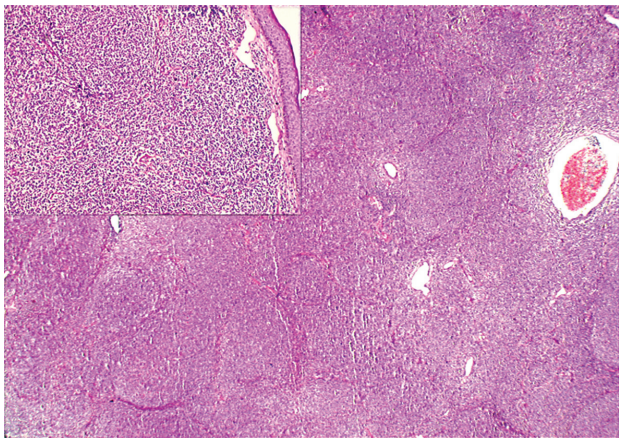

Figure 1. Back to back appearance of neoplastic follicles in cutaneous follicular B cell lymphoma (H&E ×12.5). *Inset:* Lymphoid infiltrate beneath the intact surface epithelium of the vulva (H&E ×50).

follicular dendritic cell network in the follicular areas (Figure 2). Morphological and immunohistochemical findings were consistent with primary cutaneous follicle center lymphoma (PCFCL) of B cell lineage according to the WHO-EORTC classification, 2005 [8].

Abdominal computerized tomography (CT) scan revealed a diffuse mass originating from the vulva, extending to the mons pubis and enlarged lymph nodes limited to the right inguinal region. Staging investigations included a negative bone marrow and a normal CT of the thorax. All hematological parameters including LDH were normal. IPI score was 2 and the patient had no B symptoms. The patient was diagnosed as having cutaneous NHL with a primary location in the vulva with involvement of regional lymph nodes; the stage was T2aN2M0 of the ISCL/EORTC proposal on TNM classification of cutaneous lymphomas other than mycosis fungoides/Sezary syndrome [9]. Because of her advanced age and poor performance status, the patient was treated with external beam radiation therapy alone. Radiotherapy was delivered in a parallel opposed anteroposterior technique utilizing 6 MV / 18 MV photons to a total dose of 5040 cGy in 28 fractions to the involved sites (the tumor primary site and inguinofemoral zones). With this treatment complete remission was achieved (Figures 3A and 3B). The patient is currently alive and free of disease for 18 months.

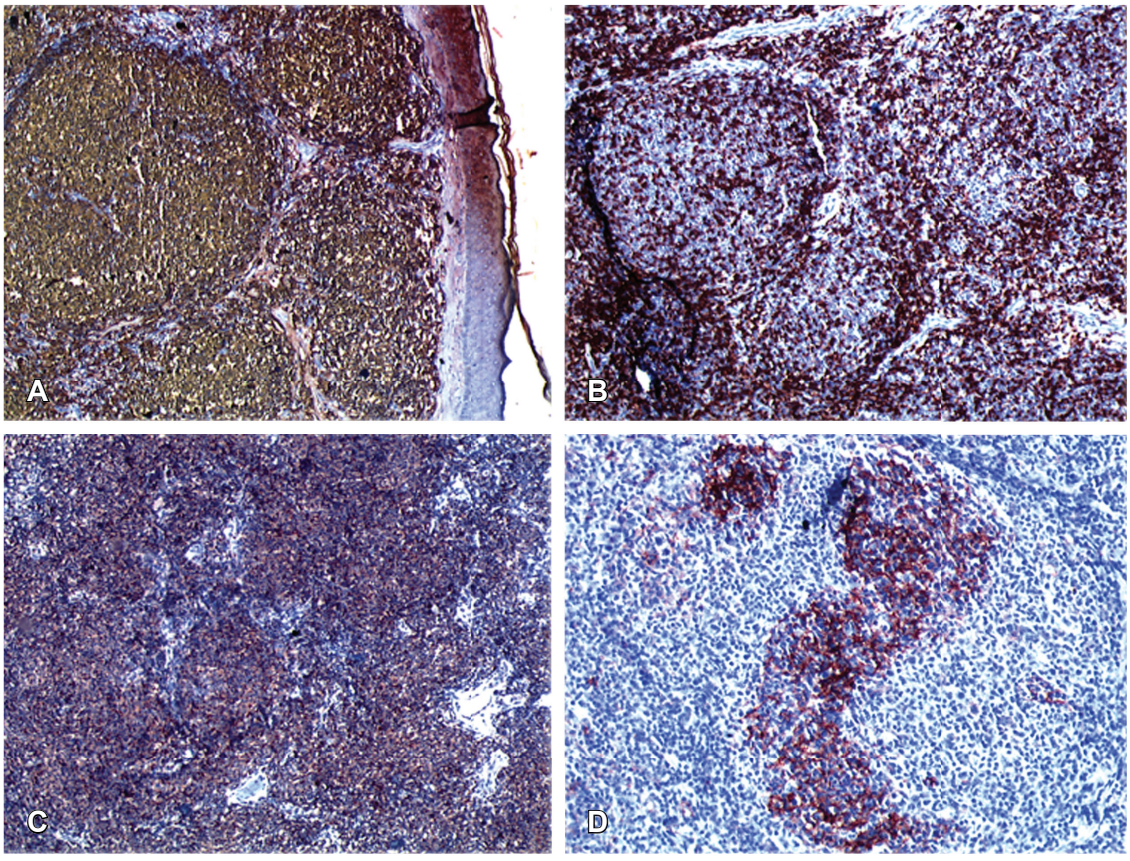

Figure 2. A: Strong CD20 immunostaining highlights the follicular pattern (CD20 IHC ×50). **B:** Note the CD3 positivity on the reactive T cells in the neoplastic follicles and in the interfollicular area (CD3 IHC ×50). **C:** Slightly pale immunostaining of bcl-2 protein on the lymphoma cells (BCL-2 IHC ×50). **D:** Irregular network of CD23 positive follicular dendritic cells (CD23 IHC ×100).

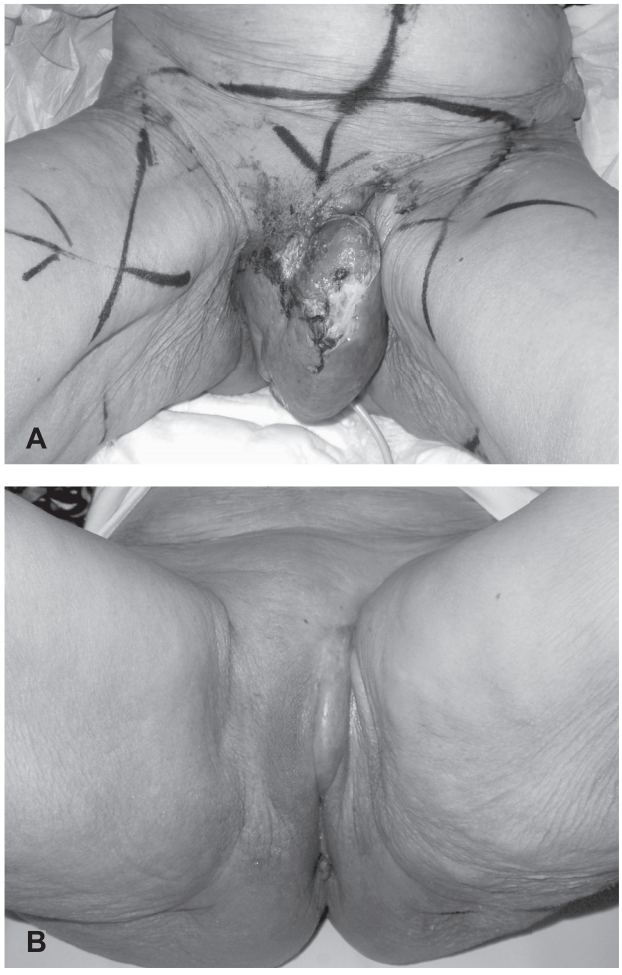

Figure 3. The appearance of the vulvar tumor: **A:** Before; **B:** A year after radiotherapy.

Discussion

Malignant lymphomas may arise in the female genital tract. The ovaries are the most commonly affected (49%), followed by the uterus (29%), fallopian tubes (11%) and the vagina (7%). Vulva is an infrequent site of malignant lymphomas (4%) [1]. Up to date, review of the English literature revealed only 20 cases of vulvar NHL of which 11 cases were primary lymphomas of B cell lineage [3,4,7,10]. Among these 11 cases only 2 were follicular large cell lymphoma with B cell immunophenotyping [6,7]. This is the third primary cutaneous follicle center cell lymphoma involving the vulvar region.

Because of its rarity, a NHL is often not considered in the differential diagnosis of a female genital tract tumor and therefore frequently misdiagnosed as a benign process or confused with other types of tumors or other inflammatory processes. Failure to make an accurate diagnosis often results in delayed treatment. As in our case, a delayed diagnosis can result in nodal lymph node involvement and a huge tumor mass.

The histological differential diagnosis for vulvar NHL includes inflammatory conditions (lichenoid dermatoses, histiocytosis, chloroma), cutaneous tumors (Bartholin's gland carcinoma, adnexal carcinomas, neuroendocrine carcinoma, lymphoepithelioma-like, poorly differentiated squamous cell carcinoma), the small cell variant of melanoma, primitive neuroectodermal tumors, rhabdomyosarcoma and malignant peripheral nerve sheath tumors [3,4,11]. Immunohistochemical stains are invaluable in aiding in the distinction of many of these entities and specifically identify the subpopulations of tumor cells - B cells, T cells, and true histiocytic cells. Thus, biopsy can be extremely valuable and should be considered in any patient with unusual clinical features. Also an atypical lymphoid infiltration in the dermis with an intact surface epithelium tends to bring to mind a diagnosis of primary or secondary NHL. However, primary or secondary lymphoma distinction resolves with the clinical history and radiological findings. In our case, as there was no evidence of extracutaneous involvement before the definite diagnosis on the incisional biopsy performed 1 year ago, the term primary cutaneous vulvar lymphoma would be appropriate for the patient. Primary cutaneous lymphomas often have completely different clinical behavior and prognosis from histologically similar systemic lymphomas which may involve the skin secondarily, and therefore require different treatment procedures [12]. For this reason a new classification system was configured for the primary cutaneous lymphomas, namely WHO-EORTC classification system [8]. Cutaneous B cell lymphomas with follicular-diffuse pattern and with centrocytic-centroblastic cells are classified as PCFCL. The morphological findings, namely follicular-diffuse pattern with mixed population of centrocytic and centroblastic cells with CD20 immunoreactivity confirm the diagnosis. On the other hand positive bcl-2 immunostaining on the neoplastic follicles remains controversial to the faint or negative staining of PCFCLs. Usually PCFCLs do not express bcl-2 protein but can show some faint staining [8]. A recent study suggests that strong expression of bcl-2 protein in the subset of PCFCL is associated with a more unfavorable prognosis [13]. This finding also correlates with the regional lymph node involvement in our patient. Despite this, the patient was successfully treated by limited field irradiation without recurrence.

Because of the rarity of vulvar NHL, there is no general consensus about the therapeutic management. The approach usually depends on the stage. Chemotherapy (CHOP regimen) is the only option in case of

advanced disease (stage III or IV). According to the literature, radiotherapy alone or in combination with surgery and / or chemotherapy appears effective treatment in stage IE or IIE [5,14]. Radiotherapy also could be restricted to the role of second-line treatment in case of incomplete response or progression during chemotherapy or in case of local relapse in young patients. More recently, rituximab, a monoclonal antibody directed against the CD20 antigen, has been added with favorable synergistic results with chemotherapy [15]. Low grade follicular lymphomas have had good cure rates with limited-field external beam radiation therapy. Although the lower grade follicular lymphomas can be treated with doses of 3500-4000 cGy, the more aggressive lymphomas require higher doses, probably because of their larger bulk, with a significant number of local relapses noticed at 5000 cGy [16]. In the present case, because of advanced age, chemotherapy was not administered to the patient but an excellent response was achieved with radiotherapy with curative intent (with 5040 cGy). The prognosis of genital lymphomas remains very good, with a 5-year survival rate ranging between 80 and 90% [3,5,14]. In contrast to nodal follicle center lymphoma, PCFCLs have a favorable prognosis with 5-year-survival rates over 90% [17]. Ferrando-Marco et al. and Signorelli et al. reported that patients diagnosed with follicular large cell lymphoma and treated with chemotherapy only remained disease-free in a 36-month follow up period, while those treated with chemotherapy and radiotherapy remained disease-free in a 247-month follow up period [6,7]. In the present case, the patient remains free of disease for 18 months following radiotherapy.

Although a gynecologist will rarely experience vulvar (genital or extranodal) lymphoma, this condition should be included in the differential diagnosis of gynecological malignancies because of a favorable outcome when properly diagnosed and treated. Based on this case, we support radiation therapy for patients with vulvar NHL who do not receive chemotherapy.

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