Case Report

Vulvar invasive squamous cell carcinoma occurring in a young woman with systemic lupus erythematosus

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Summary

Background: Although several studies have demonstrated a possible relationship between systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia and several solid tumors, it is still debatable whether SLE patients have an increased incidence of cancer overall.

Case: We describe a 25-year-old patient with SLE who developed invasive squamous cell carcinoma of the vulva. The patient underwent radical vulvectomy and bilateral groin sentinel lymph node dissection and until to date, one year after surgery, she is alive without evidence of recurrent disease.

Conclusions: Only three cases of vaginal/vulvar cancer associated with SLE have previously been mentioned in the literature, but not described in detail. This is the first detailed case report in the literature of vulvar invasive squamous cell carcinoma occurring in a SLE patient. It can only be speculated that the SLE itself and/or the treatment with immunosuppressive drugs provoked malignant transformation and the development of vulvar squamous cell carcinoma in such a young patient.

Key words: Vulvar carcinoma; Radical vulvectomy; Groin lymph nodes; Systemic lupus erythematosus; Corticosteroids; Immunosuppression.

Introduction

The association between systemic lupus erythematosus (SLE) and malignancy has as yet not been established and it is still debatable whether SLE patients have an increased incidence of cancer overall compared to the general population. Several studies, however, have demonstrated a possible relationship between SLE and non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia and several solid tumors [1-9].

We report a unique case of invasive squamous cell carcinoma of the vulva occurring in a 25-year-old SLE patient. Only three cases of vaginal/vulvar cancer associated with SLE have previously been mentioned in the literature, but not described in detail [5]. To the best of our knowledge, this is the first detailed case report in the literature of vulvar invasive squamous cell carcinoma in a SLE patient.

Case report

A 25-year-old, gravida 2, para 0, premenopausal unmarried Ashkenazi Jewish woman was admitted in August 2003 because of vulvar ulcers and pruritus of one year's duration. Menarche had occurred at age 13 and menses had been regular with a 28-day cycle and flow lasting three days. She had not practiced contraception and had two mid-trimester miscarriages. Her medical history included SLE since age 15. She had repeatedly been hospitalized in the Department of Medicine for exacerbations and complications of the SLE including nephrotic syndrome, nephritis, arthritis and pleural effusion. She had been treated for the SLE and its complications with azathioprine (imuran), high-dose prednisone, cimetidine, hydroxychloroquine, atenolol and calcium carbonate. She had never received cyclophosphamide. Her latest white blood count (WBC), serum chemistry and urine analysis were normal. Serological tests showed C3 complement, 51 mg% (normal, 90 - 180 mg%); C4 complement, 8 mg% (normal, 10 - 40 mg%); anti-DNA, 36.6 IU/ml (negative < 20 IU/ml, positive > 20 IU/ml); antinuclear antibodies, 4+; cardiolipin IgG, 5.4 GPL/ml (normal, 0 - 10 GPL/ml); cardiolipin IgM, 3.4 MPL/ml (normal, 0 - 7 MPL/ml); rheumatoid factor, negative; C- reactive protein, 3.2 mg/l (normal, 0 - 5 mg/l).

Physical examination at the time of admission disclosed an essentially healthy appearance and normal vital signs. Inspection of the external genitalia revealed multiple ulcerated nodules, each measuring 0.5 cm in greatest dimension, located on both labia minor, the inner sides of labia major and the clitoris. The lesions were mobile and not fixed to underlying tissues. The skin over the rest of the labia major was hyperemic, indurate and excoriated. The external meatus of the urethra and the vaginal orifice were not involved. No lymph nodes in either groin were palpable. Vaginal speculum examination revealed a normal-looking vagina and cervix. On bimanual pelvic examination the presence of normal internal genitalia was confirmed and no deep pelvic lymph nodes were palpable. Biopsies of the vulva demonstrated invasive moderately differentiated squamous cell carcinoma involving both sides of the vulva (Figure 1). On the left side the carcinoma measured 5 mm and penetrated to a depth of 7 mm, and on the right side the carcinoma measured 2 mm and penetrated to a depth of 1.5 mm. The carcinoma on both sides of the vulva was surrounded by multiple foci of various grades of vulvar intraepithelial neoplasia (VIN I-II-III). Computerized tomography (CT) scanning of the chest,

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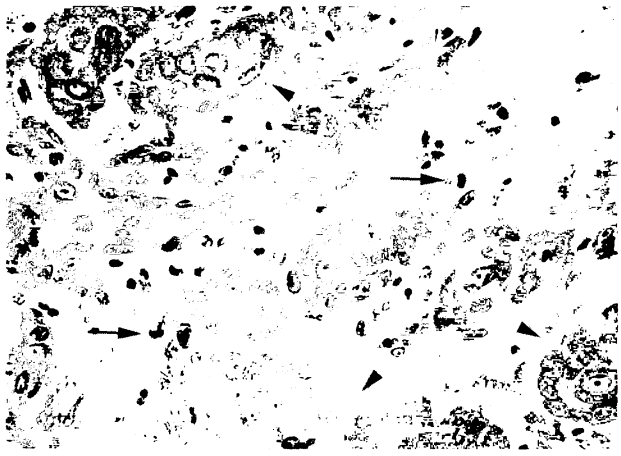

Figure 1. — Vulvar squamous cell carcinoma. Nests and tongues of moderately differentiated squamous epithelium within a desmoplastic stroma. Many mitoses (arrows) and foci of keratinization (arrowheads) are present (hematoxylin-eosin x 400).

abdomen and pelvis and ultrasound examination of the abdomen and pelvis did not show metastases. In August 2003, after stopping treatment with azathioprine and premedication with high doses of corticosteroids, the patient underwent bilateral groin sentinel lymph node identification and resection followed by radical vulvectomy. The groin sentinel lymph nodes and their afferent lymph vessels were identified after injecting the vulvar tumor with blue dye. On histopathologic examination, no tumor was found in the sentinel lymph nodes of either groin; thus, groin dissection was omitted. Histopathologic examination of the radical vulvectomy specimen demonstrated on both sides of the vulva residual invasive moderately differentiated squamous cell carcinoma measuring 1 mm and penetrating to a depth of 2 mm. The lateral margins of the vulvectomy specimen were involved with VIN I-II-III. The patient made an uneventful postoperative recovery without exacerbation of the SLE. Treatment with azathioprine was restored and corticosteroids reduced to presurgery levels. To date, one year after radical vulvectomy, the patient is alive with controlled SLE and with no evidence of recurrence of vulvar carcinoma.

Discussion

This is a unique case of invasive squamous cell carcinoma of the vulva occurring at 25 years of age in a SLE patient. Characteristically, vulvar squamous cell carcinoma most often occurs in the seventh decade of life and is rare under 50 years of age, and extremely rare under 30 years of age [10]. It can only be speculated that the disturbance of the immune system associated with the SLE itself and/or the treatment with corticosteroids and cytotoxic drugs provoked malignant transformation and the development of vulvar squamous cell carcinoma in this patient.

There are several reports in the literature dealing with the incidence of malignancy and of site-specific malignancies in patients with SLE compared to the general population [1-9, 11]. In some of these studies an increased risk of malignancy in SLE patients has been demonstrated, but the results are far from consistent and it is still debatable whether SLE patients have an increased incidence of cancer overall. An association between SLE and malignancy was first described by Cammarata *et al.* [1] in 1963. In 1976, Lewis *et al.* [2] reported a noticeable excess of malignancy in SLE patients. Pettersson *et al.* [3] reported in 1992 a statistically significant increased risk of non-Hodgkin's lymphoma, soft tissue sarcoma and overall malignancy in a cohort of 205 patients with SLE compared to the general population. On the other hand, Sweeney *et al.* [11] reported in 1995 no statistically significant increased risk of malignancy in their series of 219 SLE patients. In 1996, Abu-Shakra *et al.* [4] did not find an increased risk of overall malignancy but did show a statistically significant increased risk of hemopoietic cancer, in particular non-Hodgkin's lymphoma, in a cohort of 724 SLE patients. In 1997, Mellemkjaer *et al.* [5] reported an increased risk of both non-Hodgkin's lymphoma and solid tumors in a series of 1,585 SLE patients compared to the general population; the solid tumors were five liver cancers (relative risk (RR), 8), 15 lung cancers (RR, 1.9) and 3 vagina/vulva cancers (RR, 5.7). In 1998, Ramsey-Goldman *et al.* [6] could not find an increased risk of non-Hodgkin's lymphoma in their cohort of 616 SLE patients but did find an increased risk of breast and lung cancer. Sultan *et al.* [7] reported in 2000 that they could not show an overall increased risk of malignancy in a cohort of 276 patients with SLE; however, they did demonstrate an increased risk of Hodgkin's lymphoma compared with the general population. Nived *et al.* [12] in 2001 reported no increased risk of overall malignancy in a cohort of 116 SLE patients. In 2001, Cibere *et al.* [8] reported a statistically significant increased risk of overall malignancy (RR, 1.59; 95% confidence interval (CI), 1.05-2.32), non-Hodgkin's lymphoma (RR, 7.01; 95% CI, 1.88-17.96) and carcinoma of the uterine cervix (RR, 8.15; 95% CI, 1.63-23.81) in a cohort of 297 SLE patients compared to the general population. In 2002, Bjomadal *et al.* [9] documented 443 malignancies in a cohort of 5,715 Swedish SLE patients standing for an increase by 25% of the risk of all cancers compared to the general population (RR, 1.25; 95% CI, 1.14-1.37). The risk of non-Hodgkin's lymphoma was nearly 3-fold increased (RR, 2.86; 95% CI, 1.96-4.04) and was most pronounced early during follow-up. There was also an increased risk of lung cancer (RR, 1.73; 95% CI, 1.25-2.32) and squamous cell carcinoma of the skin (RR, 1.53; 95% CI, 0.98-2.28) which was most pronounced at more than 15 years of follow-up. In a small cohort of 29 patients with SLE, Dhar *et al.* [13] demonstrated a statistically significant increase in Pap smear reports of low-grade and high-grade squamous intraepithelial lesions (SILs) compared to control women without SLE Blumenfeld *et al.* [14] reported a significantly increased prevalence of cervical dysplasia in women with SLE.

There are no sufficient data with respect to the risk of malignancy associated with the use of cytotoxic agents in SLE and other autoimmune diseases. An increased risk of hemopoietic malignancies following azathioprine and

methotrexate therapy and an excess of bladder and skin cancers following cyclophosphamide therapy in rheumatoid arthritis have been reported by some authors [15, 16]. Two large cohort studies have not shown an increased incidence of malignancy following azathioprine or cyclophosphamide use in SLE [3, 11] and there are only a few case reports of leukemia or lymphoma following cytotoxic therapy in SLE [17, 18].

Conclusion

Only three cases of vaginal/vulvar cancer associated with SLE have previously been mentioned in the literature, but not described in detail. This is a unique case of invasive squamous cell carcinoma of the vulva occurring in a young SLE patient. It can only be speculated that the SLE itself and/or the treatment with immunosuppressive drugs caused malignant transformation and development of squamous cell carcinoma of the vulva.

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