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Leiomyosarcoma of the Vulva

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Abstract

Primary Leiomyosarcoma of the vulva is a rare mesenchymal tumor. Biologic features of a low grade tumor were investigated by an immunohistochemical workup. A 49-year-old woman presented with a slowly growing vulvar mass. Surgical treatment was performed, and a low grade leiomyosarcoma of the vulva was diagnosed. Immunohistochemical reactions were performed with monoclonal antibodies against desmin, vimentin, smooth muscle actin, cytokeratin, S-100 protein, estrogen, progesterone and androgen receptor, p53 protein, Ki-67 antigen, leukocyte common antigen and polyclonal antibodies to factor VIII-related antigen. Expression of estrogen, progesterone and androgen receptor was present in addition to a moderate number of Ki-67-positive cells and absence of p53 protein over-expression and lymphatic cell infiltration besides adequate microvessel density for smooth muscle tumors. Since the immunohistochemical markers indicated a less aggressive tumor, any further adjuvant therapy was rejected. The patient was without recurrence 30 months later. The immunohistologic profile proved the low histologic grade of vulvar leiomyosarcoma. This study is the new attempt to better understand the biology of these tumors and to estimate prognosis and plan therapy.

Key words : ulva, Leiomyosarcoma

INTRODUCTION

Primary sarcoma of the vulva is a rare tumor. The incidence of this tumor varies between 1.5 and 5% of all malignant vulvar neoplasm.[1, 2] Leiomyosarcoma is the most common histologic variant of vulvar sarcoma.[1, 2] The mean age at incidence is between 35 and 50 years (range, 15-84).[1, 2] Vulvar leiomyosarcoma is thought to derive from smooth muscle cells of erectile tissue, blood vessels, round ligament and erector-pili muscle. The tumor arises in the labium majus and the Bartholin gland area and less frequently at the clitoris or labium minus.[2] The traditional inclusion of vulvar smooth muscle tumors under the general heading of cutaneous tumors is less appropriate than classifying these tumors as an entity of their own.[3] The diagnosis is seldom established before surgical resection.

The aim of this study was to describe the clinicopathologic and immunohistochemical features of a low grade leiomyosarcoma of the vulva.

CASE REPORT

A 49-year-old Korean woman, gravida 2, para 2, was referred with a painless, slowly growing mass in the area of the Bartholin gland. The mass was detected four months before. The patient's medical history was uneventful, with regular menstrual cycles and no hormonal therapy. At the posterior part of the right labium a subcutaneous, soft mass approximately 5 cm in diameter was palpable. The clinical appearance suggested a Bartholin gland cyst. Lymph node was not enlarged in both groins and pelvic examination was normal.

At surgical exploration a yellow-gray, rubbery mass

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without connection to the vulvar skin was excised. The gross examination of the 5.5×5.0×4.5 cm tumor specimen showed a whorled, nodular, yellow-white pattern on the cut surface. In HE stains, the tumor was hypercellular, and was composed of spindle cells with intersecting fascicles. The blunt-ended nuclei had focal perinuclear clearing. Nuclear atypia and cellular pleomorphism were moderate. The mitotic count revealed 12 mitoses/10 HPF. Multinucleated cells, vascular invasion, tumor necrosis and hemorrhage were absent. Results of the immunohistochemical investigation are presented in Figure 1 and Table 1. Based on the findings, the tumor was diagnosed as low grade leiomyosarcoma of the vulva.

According to the report of malignant smooth muscle tumor with incompletely resected margins, surgical revision was performed two weeks after the primary resection. The area suspected of residua was excised with wide margins. On the cut surface of the re-excised 6.0×3.5×4.5 cm subcutaneous fatty tissue, a 1.5 cm area of gray-white tissue was seen, and it proved to be a focus of residual tumor. Tumor was absent 1cm from the resection margin.

The postoperative examination of the thorax and upper abdomen by CT scan, and magnetic resonance imaging of the pelvis revealed no evidence of metastasis. The patient is without evidence of recurrence 24 months after the resection.

DISCUSSION

To our knowledge this is the first report which attempts to comprehensively describe the biological and clinicopathologic features of vulvar leiomyosarcoma. Because of its rarity, our knowledge of this disease has been limited to sporadic case reports and rare reviews rather than large series .[1, 3, 4]

Vulvar leiomyosarcoma is relatively more common in the reproductive years. A few cases were reported in association with pregnancy.[5] This fact provides circumstantial evidence for an involvement of hormonal facotrs in the pathogenesis of this disease. Our studies lend a strong support to this hypothesis, since in the tumor cells showed strong positivity of estrogen receptors. This finding is similar to what has been noted in leiomyosarcomas of uterine origin.

It also suggests that these tumors should not be categorized under the general heading of cutaneous "pilar" smooth muscle tumors. Their usual unfavorable clinical outcome is more consistent with a behavior similar to those tumors arising in deep tissues.

Recent criteria for vulvar smooth muscle tumors are tumor size ≥ 5 cm, infiltrating margins, mitotic count > 5/10 HPF and nuclear atypia. At least three of the criteria have to be fulfilled to diagnose vulvar leiomyosarcoma .[2] In our case infiltrating margins were absent.

Prognosis is difficult to estimate. Short, aggressive or protracted courses with late recurrence have been reported. The risk of local recurrence is related predominantly to inadequate resection margins.[2]

Primary therapy has to be aimed at surgical excision with wide, free margins. Local excision is preferred to radical vulvectomy.[6] Recurrence and survival in patients treated with wide local excision are similar to those in patients treated with radical vulvectomy as initial treatment. Simple tumor excision leads to a fatal outcome. Groin dissection does not improve therapy. Whether adjuvant therapy should be offered is uncertain. In the case of tumor margin involvement at the initial surgical treatment of high grade tumor, adjuvant therapy is recommended.[2, 7] Local excision should be performed at recurrence. Irradiation improves the outcome of recurrence therapy.[2, 6] Regression of distant metastasis has been observed after chemotherapy.[6]

Recent studies have shown that biochemical and molecular markers are important adjuncts that correlate

with the behavior of sarcomas.[8)]

In normal vulvar tissue androgen receptors (AR) are markedly increased, whereas estrogen receptor (ER) and progesterone recepror (PR) decrease in comparison to vaginal tissue. The literature lacks information regarding AR expression in normal and neoplastic smooth muscle tissue of the vulva.[9)] There have been only a few cases of vulvar smooth muscle tumors where ER and PR expression was proven. Most vulvar leiomyosarcomas express steroid hormones without relation to outcome, although possibly influencing the growth of tumors.[2, 7)] Some cases are associated with pregnancy.[1, 2)] Our findings show moderate ER and strong PR and AR expression in low grade vulvar leiomyosarcoma.

Mutation of the p53 oncogene is associated with a poor prognosis in multiple malignant human neoplasms and correlates with the behavior of sarcomas. A case of high grade vulvar leiomyosarcoma presented strong expression of mutant p53 protein, whereas our low grade tumor lacked p53 overexpression.[7)]

Our case was the first report to evaluate with the expression of the cell proliferation antigen Ki-67 and Microvessel density(MVD) in vulvar sarcoma (Table 1).

Table 1. Results of the biologic profile in low grade leiomyosarcoma of the vulva.

Immunohistohemistry	Result
Actin	+
Desmin	+
Vimentin	+
AE1/AE3	-
S-100	-
Estrogen receptor [1]	4
Progesteron receptor [1]	9
Androgen receptor [1]	8
P53	-
Ki-67 [2]	320
LCA	-
MVD [3]	31

Abbreviations: AE1/AE3, a cytokeratin antibody; Ki-67, a nuclear antigen associated with cell proliferation; LCA, leukocyte common antigen; MVD, microvessel density.

[1] Immunoreactive score (range 0-12 = number of stained cells/range 0-4×staining intensity/range 0-3).
[2] Number of positive cells/10 HPF.
[3] Scored by microvessel-counting protocol.

The number of cells in uterine leiomyosarcomas expressing Ki-67 is significantly higher than in leiomyomas.[7)] Low grade vulvar leiomyosarcoma has an elevated number of Ki-67-positive cells as compared to uterine leiomyoma, although low for leiomyosarcoma. MVD does not significantly differ between benign and malignant uterine smooth muscle tumors.[7)] In vulvar leiomyosarcoma, MVD was similar to that in the uterus.

Usaually, many malignant neoplasms have a lymphocytic infiltrate, particularly at the advancing edge of the tumor. On occasion abundant lymphocytic response correlated with a better prognosis, such as the case with medullary carcinoma of the breast.[10)] In the present case, we studied the number and distribution of immune cells in the tumor. There was an abundant immune cell infiltrate throughout the tumor. Immune cells were scattered throughout the tumor with occasional aggregate formation. Lymphocytes of the B and T type were found in moderate numbers and in similar proportions. The tumor-host immunological interactions are complex. The mechanism of immune cell proliferation is not known to occur in leiomyosarcoma. One might postulate that a tumor antigenic stimulation was responsible for lymphocytic proliferation in this tumor. Further investigation of the subtype and function of the intratumoral immune cells could increase our understanding of the mechanisms involved in host immunological response to tumors.[7)]

The ultrastructural findings of actin microfilaments with interspersed dense bodies, pinocytotic vesicles, and discontinuous basal lamina support the smooth muscle origin of this tumor.

In summary, we present a unique case of a postmenopausal, obese patient who has not been on estrogen replacement therapy with a rare tumor: vulvar

leiomyosarcoma. This case is the first attempt to investigate the immunohistochemical, ultrastructural, immunological, and nuclear markers in such tumors. Our findings here are the first to demonstrate that vulvar leiomyosarcoma exhibits estrogen receptor-positivity. A variety of immune cells infiltrated the tumor with occasional lymphoid aggregate formation.

Our results help to better understand the biology of this low grade malignant smooth muscle tumor. The association of biologic features with histologic grade helps in estimating prognosis and planning therapy.

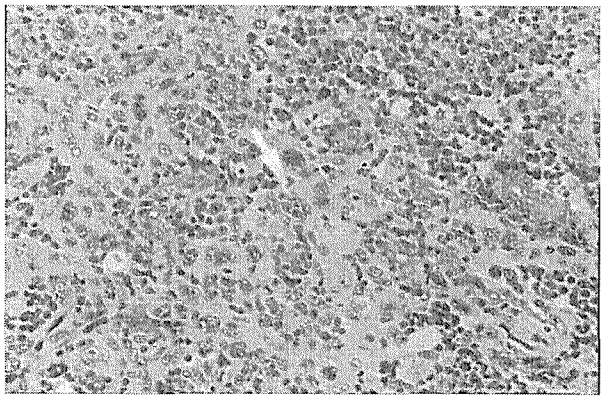

Figure 1. The tumor cell shows hyperchromatic, pleomorphic nuclei with prominent nucleoli without organoid differentiation. The inflammatory cell is infiltrated, including lymphocytes and plasma cells around tumor is noted. An arrow indicates bizarre tumor cell. (H & E, x 200).

국문초록

외음부의 원발성 자궁육종은 드문 중배엽성 종양으로서, 저 등급의 종양의 생물학적 특징은 면역조직화학적 검사 방법을 통해서 연구되었다. 외음부에 서서히 자라나는 종양을 가지고 있는 49세 여성, 수술적인 치료가 행해졌고, 저등급의 자궁육종으로 진단되었다. 면역조직화학검사로서는 desmin, vimentin, 평활근의 actin, cytokeratin, S-100 단백질, estrogen, progesterone, androgen 수용체, P53단백질, Ki-67항원, 백혈구 공통항원에 대한 단클론성 항체, Ⅷ응고인자 연관 항원에 대한 다클론성 항체 검사가 시행되었다. 적정한 수의 Ki-67양성 세포가 존재하였고, estrogen, progesterone, androgen 수용체가 발현되었으나, P53의 과발현이나 평활근섬유의 미세혈관 주위로 임파구 침윤은 없었다. 면역조직화학 표지자가 덜 공격적인 양상의 종양임을 시사하므로, 이상 부가적인 치료는 필요하지 않았다. 환자는 30개월 후까지 재발은 없었다. 면역조직화학검사로 외음부의 자궁육종의 저 등급 병변임을 규명하였다. 이러한 연구는 이들 종양의 생물학적 특성을 이해하고 예후를 평가, 치료계획 수립에 있어서 새로운 시도인 것이다. 저자들은 외음부의 자궁평활근육종을 경험하여 간단한 문헌고찰과 함께 보고하는 바이다.

중심단어 : 외음부, 자궁평활근육종

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