Leiomyosarcoma of the Vulva

Myeong Su Jeong, Wan Kyu Eo, Heung Yeol Kim

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: vulva, 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 neoplasms.\(^1\)\(^,\)\(^2\) 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
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 1 cm 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 factors 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. 6 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. 7

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
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with the behavior of sarcomas.\(^1\)

In normal vulvar tissue androgen receptors (AR) are markedly increased, whereas estrogen receptor (ER) and progesterone receptor (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.\(^5\)\(^,\)\(^7\)

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 oncoprotein 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 Microvascular density (MVD) in vulvar sarcoma (Table 1).

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

<table>
<thead>
<tr>
<th>Immunohistochemistry</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actin</td>
<td>+</td>
</tr>
<tr>
<td>Desmin</td>
<td>+</td>
</tr>
<tr>
<td>Vimentin</td>
<td>+</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>-</td>
</tr>
<tr>
<td>S-100</td>
<td>-</td>
</tr>
<tr>
<td>Estrogen receptor (^1)</td>
<td>4</td>
</tr>
<tr>
<td>Progesteron receptor (^1)</td>
<td>9</td>
</tr>
<tr>
<td>Androgen receptor (^1)</td>
<td>8</td>
</tr>
<tr>
<td>P53</td>
<td>-</td>
</tr>
<tr>
<td>Ki-67 (^2)</td>
<td>320</td>
</tr>
<tr>
<td>LCA</td>
<td>-</td>
</tr>
<tr>
<td>MVD (^3)</td>
<td>31</td>
</tr>
</tbody>
</table>

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.

Usually, 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).

REFERENCE