Case Report

Labial Aggressive Angiomyxoma Associated with Endometrial Hyperplasia and Uterine Leiomyoma: A Case Report and Review of the Literature

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A case of aggressive angiomyxoma of the left labia majora in a 48-year-old woman with clinically presenting progressive enlarged labial mass is reported. The histopathological examination of the lesion characterized was by fibroblasts, myofibroblasts in the myxoid stroma with prominent thick-walled blood vessels. The uterus showed intramural leiomyomata with simple hyperplastic endometrium. The labial mass, uterine leiomyoma and endometrial hyperplasia were immunoreactive for estrogen and progesterone receptors. Clinical and pathologic features with briefly reviewed relevant literatures were discussed. This is the first reported description in the literature of synchronous labial angiomyxoma, endometrial hyperplasia, and uterine leiomyoma.

Keywords: *Aggressive angiomyxoma, Endometrial hyperplasia, Leiomyoma, Labia majora, Estrogen*

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Aggressive angiomyxoma (AMM) is an uncommon mesenchymal neoplasm of the vulva demonstrating fibroblasts, myofibroblasts, and numerous characteristically thick-walled blood vessels embedded in an abundant myxoid matrix[1]. The various appellations have included deep angiomyxoma and pelvicoperineal angiomyxoma[1-4]. AMM generally has a benign course however locally aggressive infiltrative growth and local recurrence are not uncommon. AMM behaves an estrogen sensitive tumor, the same as endometrial hyperplasia and uterine leiomyoma. However, these three synchronous diseases have not been reported in the same patient.

The purpose of the present report was to illustrate the first published case of the labial AMM associated with endometrial hyperplasia and uterine leiomyoma on the clinical and histopathological features.

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Case Report

A 48-year-old Thai thalassemic female patient, G1P1001, living in Roiet province, Thailand came to Ramathibodi Hospital, because of a huge protruding rubbery mass with ulceration in her left major labium for two years. This mass was swelling and gradually enlarged during these two years. She had ulcers on top the mass, one month ago. There was no history of sexually transmitted disease. She had a regular menstrual period and the last menstrual period was 3 weeks ago. Physical examination revealed a healthy woman without significant abnormality. There was a swelling mass located at the 4 o'clock region of the labia majora. This mass was 20 cm in diameter, of soft consistency and had no tenderness. There were three ulcers measuring 1 to 2 cm on the surface of the mass. The vagina and cervix uteri appeared normal. The uterus had an 18-week-size. Both adnexa were free and not tender. There was no evidence of cystorectocele. The inguinal lymph node could not be palpated. A provisional clinical diagnosis was a uterine leiomyoma with the left labial tumor. Relevant laboratory investigations

included: hemoglobin 9.5 g/dL, hematocrit 30.4%, white blood cell count 10,100 per mm^3, and consisted of 56% neutrophils, 25% lymphocytes, 11% eosinophils, 7% monocytes, and 1% basophils. The liver and renal function tests were normal. Anti-human immunodeficiency virus was negative by ELISA technique. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and resection of the left labial mass were performed. The pathological diagnoses were the left labial AMM associated with uterine leiomyoma and endometrial simple hyperplasia without atypia. The postoperative course was uneventful. At the one year of follow-up, she was asymptomatic with no evidence of recurrence. She has been advised to have frequent follow-up in view of a high rate of recurrence. The present study was approved by the commitee on human research at Ramathibodi Hospital (ID 05-51-31).

Pathologic finding

The left labial tumor measuring 20 x 16 x 6 cm was obtained. The stalk was 3 x 2 x 1.5 cm. The external surface showed tan-brown skin and gray-tan nodular appearance (Fig. 1). The cut surfaces showed uniform, soft, myxoid consistency, white appearance, and ill-defined deep surgical margin. The histopathologic sections of the left labial tumor revealed numerous spindle-shaped monotonous cells loosely arranged in a myxoid matrix with intervening bundles of collagen. There was no evidence of atypical mitosis. There were abundant thick-walled blood vessels embedded in an abundant myxoid matrix. Focal extravasations of red blood cells are detected. Masson trichrome stain revealed abundant collagen. The vessels were immunoreative for smooth muscle actin, HHF35, and CD34, which stained endothelial cells, whereas the spindle cells were not. Immunohistochemical stains showed that spindle tumor cells were immunoreactive for vimentin, desmin, smooth muscle actin, HHF35, estrogen and progesterone receptors. Spindle-shaped cells were negative reactivity for S-100, sarcomeric actin, and MyoD1 (Table 1). The histopathologic findings of the endometrium showed simple hyperplasia without atypia. The myometrium showed multiple intramural smooth muscle tumors featuring whorled, anastomosing fascicles of uniform, fusiform cells. The immunohistochemical stains of the simple hyperplastic endometrium and smooth muscle tumor cells were immunoreactivity for estrogen and progesterone receptors (Fig. 2). The

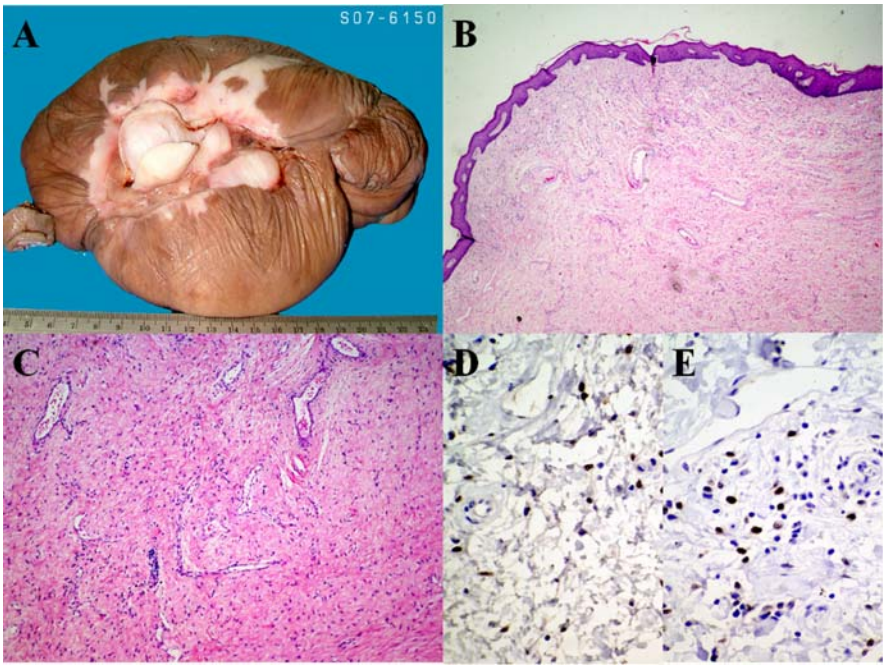

Fig. 1 The gross image shows tan-brown external surface with nodular appearance (A). The histopathologic sections of the left labial tumor reveal numerous spindle-shaped monotonous cells loosely arranged in a myxoid matrix with intervening bundles of collagen. H&E, X20 (B), X40 (C). The tumor cells show positive estrogen (D) and progesterone (E) immunohistochemical stains, X100

Table 1. Immunohistochemistry-results of primary antibodies used

Antigen	Clone	Dilution	Source	Reactivity
CD34	QBEND10	1:50	Immunotech, Marseille, France	Positive
Desmin	D33	1:100	Dako, Glustrup, Denmark	Positive
Muscle specific actin	HHF35	1:50	Dako, Carpinteria, CA, USA	Positive
Smooth muscle actin	1A4	1:100	Dako, Glustrup, Denmark	Negative
Vimentin	Vim3B4	1:200	Dako, Carpinteria, CA, USA	Positive
Estrogen receptor	1D5	1:100	Dako, Glustrup, Denmark	Positive
Progesterone receptor	PR AT4.14	1:50	Dako, Glustrup, Denmark	Positive
MyoD1	5.8A	1:50	Dako, Carpinteria, CA, USA	Negative
Sarcomeric actin	Alpha-Sr-1	1:50	Dako, Glustrup, Denmark	Negative
S-100 protein	Polyclonal	1:2000	Dako, Glustrup, Denmark	Negative

final pathologic diagnosis was the left labial AMM associated with uterine intramural leiomyomata and endometrial simple hyperplasia without atypia.

Discussion

AMM is a soft tissue neoplasm of uncertain differentiation. It is hypothesized that AMM originate from myofibroblastic and fibroblastic cells[1-4]. AMMs occur primarily in the female pelvis and perineum. The tumor occurs predominantly in the reproductive age, that estrogen may stimulate its growth. The patients have a peak incidence in the fourth decade of life[1-4]. The ages of patients range from 11 to 77 years old[5, 6]. The frequently presenting symptoms of labial AMM include labial mass or ill-defined swelling of the vulva, perineum, vagina, inguinal area, buttock, pelvis and retroperitoneum[1-4]. The sizes of AMMs describe in the literature vary from 4 to 29 cm[7]. AMM typically has locally aggressive and recurs following incomplete excision. Moreover, there are two reported cases with systemic metastasis[8,9]. The imaging procedures such as computed tomography and magnetic resonance

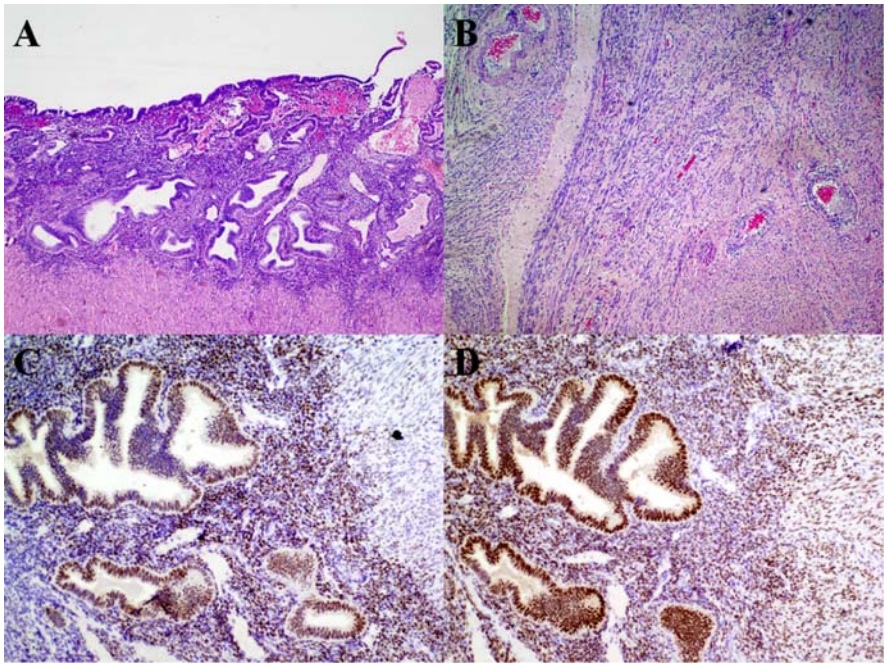

Fig. 2 The section of the uterus shows simple hyperplasia with out atypia, X40 (A), and smooth muscle tumors featuring anastomosing fascicles of uniform, fusiform cells, X40 (B). The endometrial tissues show positive estrogen and progesterone receptor, X100 (C, D)

image help in preoperative evaluation and postoperative follow-up.

The macroscopic finding of AMM is smooth, soft, partially to completely encapsulated outer surfaces. The cut surface is glistening with homogenous gelatinous appearance. Focal areas of congestion and hemorrhage are noted. The histopathologic finding consists of a fairly loose stroma composed of bland-appearing spindle-shaped cells loosely arranged in a myxoid matrix with intervening bundles of collagen fibrils. The spindle cells have small, uniformed nuclei, and indistinct nucleoli[1-4].

The histological differential diagnoses of mesenchymal neoplasms of the labia include fibroepithelial polyp, angiomyoblastoma, superficial angiomyoma, sarcoma botryoides, myxoid liposarcoma, and myxoid malignant fibrous histiocytoma (MFH)[1-4]. Fibroepithelial polyp composes of bland spindle cells in addition to enlarged, pleomorphic stromal cells with smudged chromatin. Angiomyofibroblastoma is a benign, well-circumscribed myofibroblastic lesion composing of spindle-shaped to round cells that tend to concentrate around vessels. Binucleate or multinucleated tumor cells are common and some cells have plasmacytoid appearance[1,3,4]. These findings were not found in the presented patient. Superficial angiomyoma is a multilobulated dermal lesion composed of fibroblasts and thin-walled vessels in a myxoid matrix[1,3,4]. Absence of immunoreactivity for desmin of the stromal spindle cells goes against the interpretation of superficial angiomyxoma. Sarcoma botryoides is a malignant neoplasm exhibiting striated muscle differentiation. Sarcoma botryoides occurs almost exclusively in children younger than 10 years of age and typically expresses MyoD1, and sarcomeric actin[1,3,4]. Myxoid liposarcoma has the characteristic fine plexiform vasculature and the identifiable scattered lipoblasts. Myxoid liposarcoma typically expresses S-100, but does not express estrogen and progesterone receptor proteins[1,3,4]. Myxoid MFH has a local infiltrative pattern similar to AMM. In contrast to AMM, myxoid MFH has both acellular myxoid areas rich in mucopolysacharides and more cellular areas composed of spindle-shaped cells arranged in a storiform pattern. In addition, the myxoid MFH has multinucleated giant cells, pleomorphic giant tumor cells, histiocytes, and inflammatory cells consisting of lymphocytes[1,3,4].

The pathogenesis of AMM remains enigmatic, although initially the AMM was through to represent a reactive traumatic process. However, most cases of the labial AMMs are not clearly related to trauma, they may represent chronic response or delayed presentation related to remote or undetected trauma. Currently, there are a few reports in the literature suggesting cytologic abnormality including clonal translocation t(5;8)(p15;q22), t(8;12), t(11;12)(q23;q15), loss of X chromosome, and subsequent rearrangement of the HMGIC gene[10-14]. Detection of this gene could be used as a marker of microscopic residual disease and subsequent recurrence.

AMM, uterine leiomyoma, and endometrial hyperplasia usually show diffuse nuclear immunoreactivity for estrogen and progesterone receptor proteins. These neoplasms behave as a hormone sensitive tumor and develop during the reproductive age. This concept is supported by a previous case report of rapid growth of uterine leiomyoma, and labial AMM during pregnancy[15]. Thus, there may be a role for hormone antagonist, such as selective estrogen receptor moderator.

Wide surgical excision without lymphadenectomy remains the cornerstone of management of AMMs. AMMs generally behave in an indolent manner and generally do not recur after complete surgical excision. However, this is difficult for local excision due to the tumor being non-encapsulated and has the same consistency as that of surrounding connective tissue. Some lesions that appear to be more aggressive may recur. The local recurrence rate is 30%[2]. The adjunctive therapy includes gonadotropin-releasing hormone (GnRH) agonist, which has been reported resolving labial AMMs[16,17]. Radiotherapy is generally avoided, except in advanced inoperative cases because of the risk of sarcomatous transformation. To the authors' knowledge, this is the first reported case of the synchronus labial AMM, endometrial hyperplasia and uterine leiomyoma, demonstrating positive immunohistochemical stains for estrogen and progesterone receptor proteins.

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รายงานผู้ป่วย aggressive angiomyxoma บริเวณแคมใหญ่เกิดร่วมกับภาวะการหนาตัวของเยื่อบุมดลูก และเนื้องอกกล้ามเนื้อเรียบของมดลูก

นพดล ลาภเจริญทรัพย์, พัชรีย์ การสมบัติ, ปิยนันต์ มธุรมน, ญาดา ติงธนาธิกุล

รายงานผู้ป่วยก้อนทูม aggressive angiomyxoma เกิดร่วมกับภาวะการหนาตัวของเยื่อบุมดลูก และเนื้องอกกล้ามเนื้อเรียบของมดลูกในผู้ป่วยหญิงไทยอายุ 48 ปี มาพบแพทย์ด้วยอาการก้อนที่บริเวณแคมใหญ่ข้างซ้าย ตรวจทางกล้องจุลทรรศน์พบ fibroblasts, myofibroblasts และ myxoid stroma ร่วมกับลักษณะเส้นเลือดที่มีผนังหนา โดยตรวจพบตัวรับฮอร์โมน estrogen และ progesterone ทางคณะผู้นิพนธ์ได้รายงานเรื่อง aggressive angiomyxoma ที่บริเวณแคมใหญ่ข้างซ้าย ร่วมกับทบทวนวารสารการแพทย์ที่มีการเกิดก้อนทูม aggressive angiomyxoma เกิดร่วมกับภาวะการหนาตัวของเยื่อบุมดลูก และเนื้องอกกล้ามเนื้อเรียบของมดลูกร่วมกันทั้งสามสภาวะในผู้ป่วยรายเดียว พบเป็นกรณีศึกษาแรก โดยรวบรวมวิเคราะห์การแสดงออกทางคลินิกและพยาธิวิทยา