Case Report

Leiomyosarcoma with Osteoclast-Like Giant Cells of the Uterus: A Case Report and Literature Review

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The presence of osteoclast-like giant cells (OGC) has been reported as a rare and distinct feature in uterine leiomyosarcoma. To present knowledge, 11 cases have been described in the English literature. The authors report an additional example in a 35-year-old woman who presented with a pelvic mass. Pulmonary metastasis was detected by the preoperative CT scan. The hysterectomy specimen revealed a 11.5 cm intramural mass with hemorrhagic and necrotic center. The histologic examination revealed pleomorphic sarcoma with OGC. The neoplastic cells were immunoreative for smooth muscle actin and desmin. Minor intermixing component of conventional leiomyosarcoma and leiomyoma were identified at the periphery of the malignant component. The patient died of disease after 16 months of diagnosis. To our knowledge, this is the youngest case of uterine leiomyosarcoma with OGC. Leiomyosarcoma with OGC has an aggressive clinical course. The tumor may occur in young patient and may arise from pre-existing leiomyoma.

Keywords: *Uterus, Leiomyosarcoma, Osteoclast-like giant cells, Leiomyoma*

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Although leiomyosarcoma comprises slightly over 1% of uterine cancers, it is the most common malignant mesenchymal tumor of the uterus[1]. The presence of osteoclast-like giant cells (OGC) has been reported as a rare and distinctive feature in uterine leiomyosarcoma, and may be considered as a morphologic variant[2]. To our knowledge, eleven cases of leiomyosarcoma with OGC of the uterus have been reported[2-12]. The authors present an additional case of uterine leiomyosarcoma with OGC, with a review on the clinicopathologic features of these tumors.

Case Report

A 35-year-old woman presented with a pelvic mass that has been enlarged for three months. There was no abnormal vaginal bleeding. The physical examination and the abdominal Computed Tomography (CT) scan showed a solid-cystic mass in the pelvis, which could be of either ovarian or uterine origin. Two small nodules, 0.6 cm each, were noted in the left lower lung, consistent with metastatic lesions. The patient underwent an exploratory laparotomy that revealed an enlarged uterus. Resection of the uterus and biopsy of pelvic and para-aortic lymph nodes were performed. The sectioned surface of the uterus showed an 11.5 cm intramural mass in the posterior wall. The mass was well-circumscribed and composed of solid soft and fleshy pink-tan tissue with large central necrotic and hemorrhagic area. At the posterior aspect of the mass, there was a 9 x 3 cm peripheral crescentic area of firm white tissue with whorl-like appearance (Fig. 1). The tumor was grossly confined within the myometrium without serosal involvement or peritoneal spread.

The histologic examination revealed high grade and hypercellular malignant tumor composed of oval to spindle-shaped cells with marked nuclear pleomorphism. In approximately 90% of tumor tissue, there were interspersed multinucleated giant cells of osteoclast-like type between the malignant cells (Fig. 1). The giant cells contained many nuclei that were uniform and oval-shaped with single distinct nucleoli, in contrast to the surrounding malignant cells. The mitotic count was 51 in 10 high power fields in the most active area. At the periphery of the mass, there were

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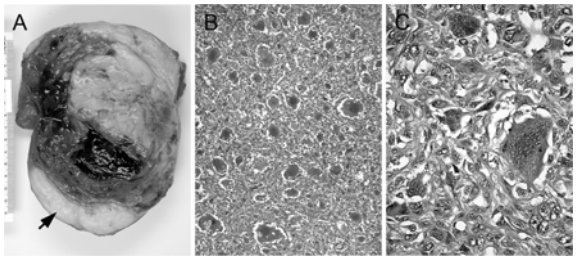

Fig. 1 Uterine leiomyosarcoma with osteoclast-like giant cells. A, Sectioned surface shows a large intramural mass with extensive hemorrhagic center. A peripheral crescentic area (arrow) with firm and whorl-like cut surface represents a residual portion of leiomyoma. Uninvolved myometrium is seen at the top right. B and C, Histologically, numerous multinucleated giant cells with osteoclast-like features are interspersed between pleomorphic sarcomatous cells

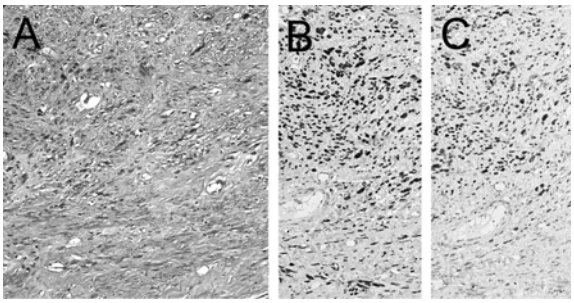

Fig. 2 Transition between conventional leiomyosarcoma (top) and leiomyoma (bottom). A, The sarcomatous part shows pleomorphic nuclei. B, Both components show diffuse immunoreativity for progesterone receptor. C, Diffuse p53 immunoreactivity is confined only to leiomyosarcomatous component

intermixing foci of usual leiomyosarcoma characterized by pleomorphic spindle cells with eosinophilic cytoplasm, arranged in interlacing fascicles. The area corresponding to white firm peripheral crescent on gross examination represented a residual portion of leiomyoma that merged with the inner zone of conventional leiomyosarcoma. The merging zone between conventional leiomyosarcoma and typical leiomyoma had an appearance similar to atypical leiomyoma with the absence of mitotic figures (Fig. 2). The immunohistochemical profile of all tumor components is presented in Table 1. The sarcomatous cells showed immunoreactivity for desmin and alpha-smooth muscle actin, whereas the giant cells were immunoreactive for CD68 (diffuse and strong) and CD45 (focal). Involvement of many lymphovascular spaces by sarcomatous tissue with OGC was observed, as was a microscopic metastatic focus in the left parametrial soft tissue. The pelvic and para-aortic lymph node showed no metastatic involvement.

Postoperatively, chemotherapy was given consisting of ifosfamide and adriamycin for six courses. At the completion of chemotherapy, disappearance of the pulmonary nodules in the left lower lung was noted on the follow-up chest and abdominal CT scan. No definite evidence of metastasis at the other sites was observed. After nine months of regular follow-up, a 4-cm mass was detected above the vaginal stump.

Table 1. The immunohistochemical profile of smooth muscle tumor cells and osteoclast-like giant cells (OGC)

Antibody	Source, dilution, and antigen retrieval method	Smooth muscle components			Osteoclast-like giant cells
		Typical leiomyoma	Malignant (conventional type)	Malignant with OGC	
Desmin	Dako, 1:100, MW	++++	++++	++	0
Smooth muscle actin	Dako, 1:1,000, MW	++++	++++	+	0
Estrogen receptor	Dako, 1:200, PC	+++	+++	0	0
Progesterone receptor	Dako, 1:200, PC	++++	++++	0	0
p53	Dako, 1:2,000, PC	0	++++	++++	0
Ki-67	Dako, 1:200, PC	0	Variable (0 to ++)	++	0
CD68	Dako, 1:500, MW	0	0	0	++++
CD45	Dako, 1:1,000, MW	0	0	0	++

MW: microwave, PC: pressure cooker,
0: negative or ≤ 5% positive cells, + : 6-10% positive cells, ++ : 11-50% positive cells, +++ : 51-90% positive cells, ++++ : > 90% positive cells

The chest roentgenogram showed multiple metastatic nodules, up to 2.8 cm in diameter, in the left lower lung. She received another six courses of cisplatin as a palliative chemotherapy and there was no progression in size of the metastatic lesions. After cessation of chemotherapy for a month, multiple subcutaneous nodules were detected at the extremities and the trunk. The CT scan showed multiple metastatic lesions in both lungs, anterior mediastinum, left adrenal gland, pancreas, both kidneys, and the pelvic cavity. As she had poor performance status, no further specific treatment was given. She died of disease 16 months after diagnosis.

Discussion

The presence of OGC is a distinctive morphologic feature reported in malignancies of various origins and histologic types, including carcinomas (*e.g.* breast, pancreas, etc) and sarcomas[4]. Carcinomas with OGC of the breast and the pancreas have been recognized as morphologic variants in the World Health Organization Classification[1,13]. Among sarcomas, pleomorphic sarcoma with OGC used to be recognized as giant cell variant of malignant fibrous histiocytoma. Immunohistochemical studies have now demonstrated that most of such tumors actually represent other specific types of sarcoma, with leiomyosarcoma being an important group[14,15]. In addition to the uterus, leiomyosarcomas with OGC have been reported in soft tissue, gastrointestinal tract, adrenal gland, and heart[14,16-18]. The origin of OGCs has been proposed to be a reactive response of histiocytic cells, supported by their different immunohistochemical profile (CD68+ and CD45+ or -) from surrounding malignant cells[14]. Furthermore, osteoclastic differentiation of tumor-associated macrophages isolated from breast carcinoma can be induced under in vitro circumstance[19]. The presence of OGC is typically associated with high-grade malignant features characterized by marked nuclear pleomorphism with high mitotic index and central areas of necrosis or hemorrhage.

Table 2 shows a summary of clinicopathologic features and treatment results of uterine leiomyosarcoma with OGC in 12 cases. Most patients having uterine leiomyosarcoma with OGC were postmenopausal with a mean age of 55 years. Only two cases occurred in premonopausal age group (35 and 45 years) with the present case being the youngest. Two-thirds of the patients with available data presented with abnormal uterine bleeding. Furthermore, two-thirds of these also had uterine curettage positive for malignancy. Prolonged fever was reported as an unusual presentation in one case, probably due to certain cytokine production[9]. The occurrence of tumor in young patient reported here is uncommon for either conventional uterine leiomyosarcomas or leiomyosarcomas with OGC. In other organs, leiomyosarcomas with OGC almost exclusively occurred in the patients of old age group (usually > 60 years)[14,16].

Transformation of uterine leiomyoma into leiomyosarcoma is generally considered as an uncommon phenomenon[1]. In cases with OGC, benign smooth muscle components (including atypical leiomyoma) were identified in four of 10 cases including ours (40%), with three of these having obvious gross benign portion[8,9,12]. In the other six cases, association of leiomyosarcoma with OGC with usual leiomyosarcomatous component was reported, as an intermixing component in five cases[2-5,7], and as an adjoining mass in the remaining case[6]. The findings support that uterine leiomyosarcoma with OGC may originate from pre-existing better-differentiated smooth muscle tumor component in a similar manner to the so-called 'pleomorphic leiomyosarcoma' in the soft tissue[20].

The immunohistochemical expression of estrogen/progesterone receptor, Ki-67, and p53 protein have been reported to help in the distinction between benign and malignant smooth muscle tumors[21,22]. Leiomyomas are more likely to have high expression of estrogen/progesterone receptor but low Ki-67 proliferative index and p53 expression. The immunoprofile in the typical leiomyomatous portion in the current case supported that this component should not represent the well-differentiated part of leiomyosarcoma. The presence of transitional morphologic change from leiomyoma to leiomyosarcoma suggested that leiomyoma was a precursor lesion of malignancy, whereas the OGC-containing component represented more progressive dedifferentiation. Both conventional type and leiomyosarcoma with OGC showed very high index of p53 overexpression, which was likely to be associated with the presence of p53 mutation[23]. High p53 overexpression was also seen at the transition between leiomyoma and leiomyosarcoma, which had an atypical leiomyoma-like appearance, suggesting that p53 mutation may be an early event in the carcinogenesis.

The prognosis of uterine leiomyosarcoma with OGC seems to be worse than high-grade uterine leiomyosarcoma of conventional type[24]. The presence

Table 2. Summary of clinicopathologic features and treatment results of uterine leiomyosarcoma with osteoclast-like giant cells in 12 cases, arranged in order of tumor stage and clinical outcome

Case report (first author)	Age (year)	Presenting symptom	Curettage result	Size (cm)	Associated smooth muscle tumor component	Tumor stage* (site of spread)	Treatment	Outcome (duration)
Mallory1[1]	NA	NA	NA	NA	NA	NA	NA	NA
Evans1[2]	NA	NA	NA	NA	Atypical leiomyoma	NA	NA	ANED, 10 yr
Evans[10]	NA	NA	NA	NA	NA	NA	NA	DOD, 3 mo
Watanabe[7]	56	Bleeding	NA	8	Leiomyosarcoma	I	Surgery	NA
Patai[9]	54	Fever	Negative	6**	Cellular leiomyoma	I	Surgery	ANED, 12 mo
Darby[3]	53	Bleeding	Positive	NA	Leiomyosarcoma	I	Surgery	ANED, 6 mo
Pilon[5]	82	Bleeding	Positive	10	Leiomyosarcoma	I	Surgery RT	Vagina +, 3 mo DOD, 17 mo
Aru[8]	45	Bleeding	Not done	10**	Leiomyoma	I	Surgery CT	Pelvis & lung +, 3 mo DOD, 5 mo
Chen[2]	59	Bleeding	Positive	3.5	Leiomyosarcoma	IV (omentum)	Surgery & RT CT	Lung +, 4 mo DOD, 21 mo
Marshall[4]	55	Abdominal pain & vaginal discharge	Negative	13	Leiomyosarcoma	IV (omentum, bowel)	Surgery	DOD, 4 mo
Present case	35	Pelvic mass	Not done	11.5	Leiomyosarcoma and leiomyoma	IV (parametrium, lung)	Surgery & CT CT	Vagina & lung +, 9 mo DOD, 16 mo
Sienski[6]	56	Bleeding	Positive	7	Adjacent leiomyosarcoma (6.5 cm)	IV (omentum, lung)	Surgery CT	Vaginal/vulvar +, 12 d DOD, 81 d

* The FIGO staging of cancer of the uterine corpus as applied to uterine leiomyosarcoma[24]

** Size of the entire mass including benign part, the malignant component was confined only to the central portion

ANED: alive with no evidence of disease, CT: chemotherapy, DOD: dead of disease, HPF: high power fields, NA: not available, RT: radiation therapy

of adverse prognostic factors in tumors with OGC such as large tumor size, marked nuclear atypia, high mitotic rate, and advanced stage may contribute to such poor patients' outcome. The patients with extrauterine spread at presentation died of metastatic disease within 2 years despite combined surgery and adjuvant therapy (Table 2). However, confinement to the uterus (stage I, if the FIGO staging of cancer of the uterine corpus would be applied[24]) and a small tumor size did not predict a good prognosis as reported by Aru et al[8]. In that fatal case, the malignant component was confined to the center of a 10-cm leiomyoma and was detected in only five of 95 sections (~ 5%) of the mass[8]. This finding suggests that leiomyosarcoma with OGC is highly capable of dissemination and may metastasize early. On the other hand, three cases were reported to be alive and well (6 months to 10 years), two of these were known to be of stage I and did not receive any adjuvant treatment after surgery. Therefore, it may be difficult to predict the prognosis of stage I tumor in each individual patient. In the other six cases (stage I-IV) with available data, disease progression was detected within four months postoperatively in five patients who did not receive initial postoperative chemotherapy[2,5,6,8], whereas in our case, who received such chemotherapy, the progression was detected nine months after diagnosis. The delay in disease progression, as well as some response to chemotherapy (cyclophosphamide, adriamycin, and cisplatin) in the case reported by Chen[2], supports the beneficial role of postoperative chemotherapy in the treatment of leiomyosarcoma with OGC, although the effective regimen may remain to be determined.

In conclusion, leiomyosarcoma with OGC is a morphologic spectrum of high-grade leiomyosarcoma with aggressive behavior. The tumor may occur in young patient and may arise from pre-existing leiomyoma. Careful examination of any uterine leiomyoma is warranted as this aggressive tumor may sometimes be a minor component in leiomyoma.

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มะเร็งกล้ามเนื้อมดลูกที่มีเซลล์ยักษ์ชนิด osteoclast-like: รายงานผู้ป่วย 1 ราย และทบทวนวรรณกรรม

กรกนก สุขพันธ์, สุรพันธุ์ คุณอมรพงศ์, ประภาพร สู่ประเสริฐ, สุมาลี ศิริอังกุล

มะเร็งกล้ามเนื้อมดลูกที่มีเซลล์ยักษ์ชนิด osteoclast-like พบน้อยมากและมีลักษณะเด่นชัด มีรายงานในวารสารเพียง 11 ราย รายงานนี้นำเสนอผู้ป่วยหญิงอายุ 35 ปี มีอาการนำ ได้แก่ ก้อนในอุ้งเชิงกราน การตรวจภาพถ่ายรังสีพบมะเร็งกระจายไปที่ปอด การผ่าตัดมดลูกพบก้อนมะเร็งขนาด 11.5 เซนติเมตร ที่มีเลือดออกและเนื้อตาย การตรวจทางจุลพยาธิวิทยาพบเซลล์มะเร็งที่มีลักษณะ pleomorphic ร่วมกับเซลล์ยักษ์ชนิด osteoclast-like เซลล์มะเร็งให้ผลบวกเมื่อย้อมพิเศษทางอิมมูโนต่อ smooth muscle actin และ desmin และพบส่วนของมะเร็งกล้ามเนื้อมดลูกชนิดธรรมดาร่วมกับเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ร้ายที่ขอบก้อนมะเร็ง ผู้ป่วยเสียชีวิต 16 เดือนหลังการวินิจฉัย ผู้ป่วยรายนี้มีอายุน้อยที่สุดเท่าที่มีรายงาน มะเร็งกล้ามเนื้อมดลูกที่มีเซลล์ยักษ์ชนิด osteoclast-like เป็นมะเร็งที่มีการดำเนินโรคร้ายแรง สามารถพบในผู้ป่วยอายุน้อย และอาจเกิดขึ้นจากเนื้องอกกล้ามเนื้อมดลูกชนิดไม่ร้าย