

C A S E R E P O R T

Case report of atypical endometrial stromal cells in an endometrial polyp and osteoclastic like giant cells in leiomyoma in the same patient: Is it a coincidence or is it a result of Tamoxifen treatment?

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Summary. Atypical stromal cells are rarely identified in the endometrial polyps of the female lower genital system. These cells are suggested to develop due to a degenerative or reactive phenomenon. And osteoclastic like giant cells, which have been reported in many epithelial and mesenchymal tumors of uterus, may develop because of a degenerative or a reactive process. In this case report, we present a breast cancer patient who was commenced on Tamoxifen treatment presenting with formation of both atypical stromal cells in an endometrial polyp and osteoclastic like giant cells in the leiomyoma of the uterus. Patients who are treated with Tamoxifen should be followed meticulously to detect tumoral or proliferative lesions of endometrium and myometrium because of the adverse effects of tamoxifen on uterus. (www.actabiomedica.it)

Key words: atypical endometrial stromal cells, osteoclastic like giant cells, leiomyoma, tamoxifen treatment

Introduction

Fibroepithelial polyps of the female lower genital system are periodically observed while atypical stromal cells are very rarely reported as a feature of the endometrial polyps (1). Atypical stromal cells are described for the first time in an endometrial hyperplastic polyp in 1995 by Creagh et al (2). These cells are stellate and enlarged, display moderately to severely atypical, hyperchromatic, multilobulated nuclei, and have little proliferative activity with no mitoses (3). Atypical stromal cells inside the endometrial polyps are suggested to develop due to a degenerative or reactive phenomenon (1).

Tamoxifen which has antiestrogenic properties, exerts a weak estrogenic effect on human endometrium leading to a spectrum of endometrial proliferative lesions like polyps, simple/complex atypical hyperplasia, and even adenocarcinomas, depending on the patients'

menopausal status; as well as on the dose and duration of tamoxifen usage (4).

Osteoclastic like giant cells have been reported in various epithelial and mesenchymal tumors in various anatomic locations including uterus (5). Except for the malignant tumors in literature; there is one case revealing osteoclastic like giant cells in uterine leiomyoma (5).

In this case report, we present a breast cancer patient who was commenced on tamoxifen treatment that led to the formation of both atypical stromal cells in an endometrial polyp and an osteoclastic like giant cells in the leiomyoma of the patient.

Case report

Our patient is a 53 years old woman, who is Caucasian in origin. In 2013, radical mastectomy procedure

had been performed for invasive ductal carcinoma of breast. After surgery, 10 cycles of chemotherapy were given to the patient. Following chemotherapy, she used Tamoxifen between 2014 and 2017. The dose of Tamoxifen was 20 mg/day. She had no any other disease in her general examination. Before using Tamoxifen, transvaginal ultrasonography had been performed, and everything was normal in her ultrasonography. She did not have any complaint in her follow-ups. She was admitted to the gynecology and obstetrics clinic for pelvic pain in November 2016. After her physical examination and transvaginal ultrasonography examination and her endometrium was found thickened in ultrasonography. Therapeutic curettage was performed due to this increase in endometrial thickness. In histopathological examination of this curettage specimen, significant stromal atypical cells were detected in the superficial endometrial stroma. These atypical cells were stellate, spindle and enlarged cells. Their nuclei were hyperchromatic and had no mitoses. The cells revealed dense chromatin with prominent nucleoli (Figure 1, 2). Immunohistochemically CD10 was positive in the atypical stromal cells while H-caldesmon and pan cytokeratin were negative in these cells. However, these atypical stromal cells in the curettage specimen were so scarce that these cell groups were not apparent in the proceeding sections of the specimen. With immunohistochemical and morphological findings the curettage specimen was reported as suspicious for ma-

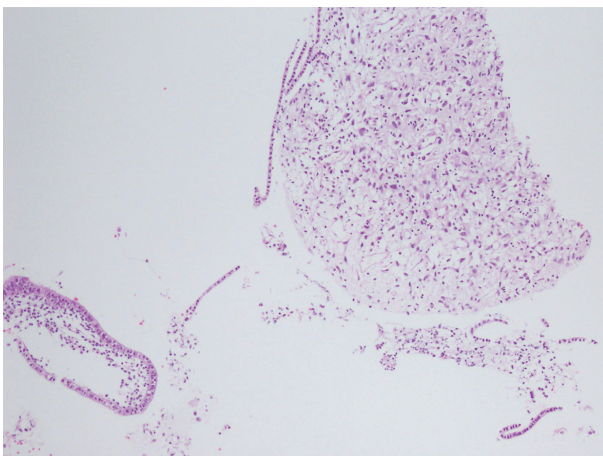


Figure 1. Small atypical stromal cell group in curettage specimen (HE X 100)

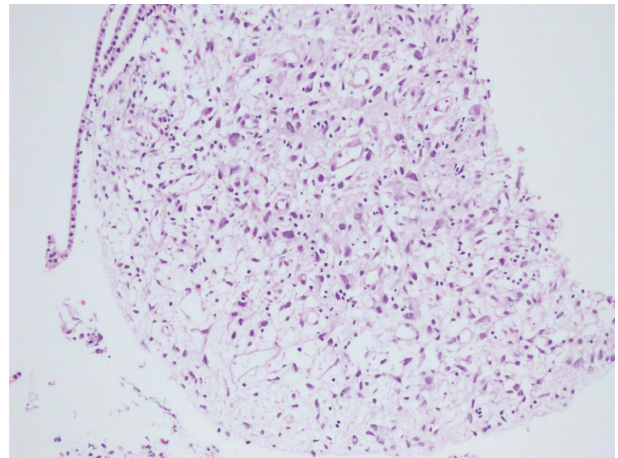


Figure 2. Pleomorphic, enlarged stellate cells with hyperchromatic nucleus (HE X 200)

lignancy with the differential diagnosis of adenosarcoma and high-grade stromal sarcoma. Total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. In the macroscopic examination of the patient's uterus: a 5×2,5×1,5 cm grey-brown colored polypoid lesion was detected in the endometrial cavity. In the hysterectomy specimen of the patient there were three intramural white, fasciculate nodules, measuring between 1 and 6 cm in diameter. These intramural nodules did not have any necrotic or hemorrhagic areas. Any other significant atypia was found in the endometrial polyp. The findings were compatible with classical endometrial polyps (Figure 3).

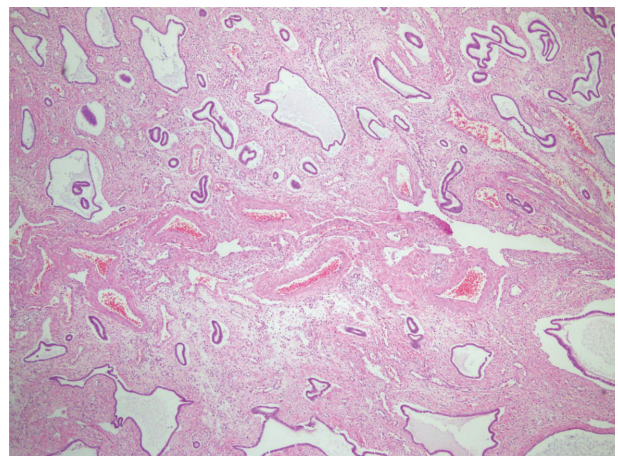


Figure 3. Classic appearance of endometrial polyp in resection (HEx40)

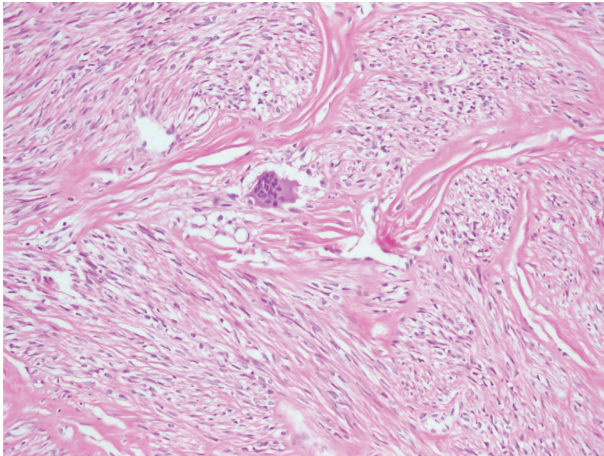


Figure 4. Osteoclastic like giant cell in the leiomyoma section (HE X 200)

The cervix, fallopian tubes and ovaries were ordinary. One of the leiomyomata, measuring 3.7 cm, had infrequent benign-appearing osteoclastic like giant cells between the smooth muscle fibers. Osteoclastic like giant cells were diagnosed morphologically (Figure 4). The uterus specimen was histopathological reported as an endometrial polyp and leiomyoma with osteoclastic like giant cells. After the operation, the patient had been examined with transabdominal ultrasonography again. So far, she had no other complaint.

Discussion

Fibroepithelial polyps of female the lower genital system is frequently observed, and atypical stromal cells are rarely present as a feature of the endometrial polyps in patients ranging from 24 years to 86 years (1). However, these cells have been rarely described in proliferative endometrium without polyps (6). Atypical stromal cells of the lower genital tract were first described in vagina by Norris and Taylor (2). Later these cells were reported in the vulva and cervix (7). In 1992 a case of bilateral fibroepithelial polyp of labia minora containing atypical stromal cells was published (2). Creagh et al, described this phenomenon for the first time in 1995 in an endometrial hyperplastic polyp (2). Tai et al, reported 15 cases with an average age of 59.7 years in 2002 (2). In this report, 12 patients were

in post-menopausal period and five patients had hormone replacement therapy history (2).

Atypical stromal cells are stellate and enlarged cells (3). Their nuclei are moderately to severely atypical, hyperchromatic, multilobulated, and show little proliferative activity with no mitoses (3). They have dense chromatin and prominent nucleoli (3). Pseudo inclusions may be present (2, 3). Cells are invariably positive for vimentin, estrogen, androgen, and progesterone receptors occasionally and focally for CD10 which is a frequent endometrial stromal marker for smooth muscle markers such as actin, desmin, h-caldesmon and occasionally for S100 which is a Schwann cell and lipid cell marker (3). On the other hand, atypical stromal cells are consistently negative for cytokeratin, epithelial membrane antigen, myogenin, CD34, antichymotrypsin, Factor VIII, and lysozyme (3).

The origin of atypical stromal cells is controversial (2). They are suggested to originate from fibroblasts and their differential potential into both endometrial stromal and smooth muscle cells has been documented (8). It is thought that these cells consist of a primitive cellular population originating from the multipotent mesenchymal cells (8). Atypical stromal cells inside the endometrial polyps develop due to a degenerative or reactive phenomenon like in atypical (bizarre) leiomyoma (1). In order to explain the pathogenesis of these cells, several hypotheses have been proposed. One of them is that the mast cells may play a role in the formation of multinucleated stromal cells because these cells are essential for the development of inflammation, fibrosis, and angiogenesis (9). In addition to these hypotheses, because of the electron microscopical findings and reaction with S100 antibody, atypical stromal cells are thought to originate from peripheral nerve sheath (10). Besides these hypothesis, atypical stromal cells may also have either a smooth muscle or an endometrial stromal immunophenotype (6).

Because the curettage material with limited specimen volume, differential diagnosis of atypical stromal cells from adenosarcoma, endometrial stromal sarcoma, and carcinosarcoma/malignant mixed Mullerian tumor (MMMT) is crucial and must be meticulously done (8). Atypical stromal cells are distinguished from adenosarcoma by the lack of stromal hypercellularity, peri glandular stromal cuffing, cambium layer beneath

the surface epithelium, leaf like projections into the glandular lumina, increased stromal mitotic activity which is >3 mitosis/10HPF and sarcomatous stromal overgrowth with homologous and/or heterologous elements (2). Differentiation from endometrial stromal sarcoma is by endometrial stromal sarcomas appearance as a mass lesion with infiltrative borders (2). Endometrial stromal sarcomas are tan to yellow and can be bright orange in color. Microscopically they are composed of tightly packed spindled cells without significant glandular component (2). There are small capillaries distributed evenly in these lesions (2). Occasionally, starburst hyalinization is noted (3). Endometrial stromal sarcomas of uterus present as worm like masses throughout the uterus and typically do not form pure polypoid lesions, although they may have a polypoid component (8). Atypical cells are extremely rare in endometrial stromal sarcomas (8). Malignant mixed Mullerian tumor is a rare neoplasm, also termed uterine carcinosarcoma comprising only 1-2% of uterine neoplasms (11). These tumors are a dedifferentiated or metaplastic form of endometrial carcinoma (12). This tumor reveals both glandular and stromal components (2). Sarcomatous component may contain homogenous and/or heterogenous elements (2). The characteristic microscopic feature is an intimate admixture of malignant epithelial and stromal elements (11). Although increased mitotic activity among the atypical cells is supportive for carcinosarcoma in a curettage or biopsy sample, the possibility of MMMT is difficult to exclude because of the fragmented nature of the specimen and the possibility of sampling error (2).

Tamoxifen is a nonsteroidal triphenylmethyl compound that is used as adjuvant therapy in the treatment of breast cancer patients (4). It is a selective estrogen receptor modulator (SERM) and prolongs overall and disease-free survival in breast cancer (13). It reduces the likelihood of disease development in the contralateral breast and also may reduce the risk of development of breast cancer in asymptomatic women with a strong family history (13). Tamoxifen affects by anti-estrogenic properties that are mediated by competitive binding to the estrogen receptor (4). However, it also has a weak estrogenic effect on human endometrium (13). The endometrium of postmenopausal patient who use tamoxifen is significantly thicker than that of

age matched group who do not use tamoxifen (14). Ki-67 proliferation index is higher in such patients (14). Tamoxifen results in a spectrum of endometrial proliferative lesions like polyps, simple/complex atypical hyperplasia, and even adenocarcinomas (4, 14). McCluggage et al, reported that high grade endometrial cancers including serous carcinomas and carcinosarcomas are more frequent in patients using tamoxifen (15). They also revealed that uterine leiomyosarcomas, endometrial stromal sarcomas, adenofibromas, and adenocarcinomas may occur in patients using tamoxifen (15).

Osteoclastic like giant cells have been reported in numerous epithelial and mesenchymal tumors in various anatomic locations mostly in uterus. They are present in endometrial carcinoma, endometrial Adenocarcinoma, endometrial stromal sarcoma, extrasosseous malignant giant cell tumor and malignant fibrous histiocytoma and leiomyosarcoma (16, 17). Except for the malignant tumors in the literature; there is one case revealing osteoclastic like giant cells in uterine leiomyoma (5). In this case Guilbert et al, have described benign appearing osteoclastic like giant cells in a leiomyoma, measuring was 3,5 cm. These cells were admixed with smooth muscle bundles (5). Bizarre multinucleated giant cells have been reported in atypical leiomyomas (5). But in contrast to osteoclastic like giant cells's monotonous morphological features, multinucleated giant cells in bizarre leiomyoma show varying degree of pleomorphism and nuclei atypia (5). Osteoclastic like giant cells's origin is still unclear. Although morphologically they resemble to osteoclasts, the origin of these cells seems to be histiocytic in origin as shown by immunohistochemical and ultrastructural studies (18). Thus, these cells may occur as a stromal reaction to tumoral cells and tumoral biochemical microenvironment.

In summary, tamoxifen may lead to stromal reactions as we have observed in this case. Osteoclastic like giant cells may occur in such patients. Atypical stromal cells were also present in the endometrium. Tamoxifen commitment may lead to the development of atypical stromal cells in the endometrial polyp and osteoclastic like giant cells in the leiomyoma. Clinicians should bear in mind that the above pathologic changes may occur as a manifestation of tamoxifen treatment. These patients should be followed meticulously to detect en-

dometrial and myometrial, tumoral, or proliferative lesions.

Ethics: The patient has been confirmed that written informed consent which include the case details. The patient also has confirmed about her published histopathological images.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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