Possible Relationship Between Tamoxifen Therapy and Vaginal Angiomyofibroblastoma

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Angiomyofibroblastoma is an uncommon, benign, mesenchymal tumor which was first described by Fletcher et al.[1] in 1992. The characteristics include well-circumscribed margins and prominent vascularity with neoplastic cells exhibiting features suggestive of myofibroblastic differentiation.[1] The tumor predominantly arises in vulva while vaginal location is extremely rare and only 11 cases have been reported so far in the English literature.[2-11]

We identified another case who had a history of infiltrative ductal carcinoma of breast and had undergone a left modified radical mastectomy 2 years ago followed by radiotherapy and combined chemotherapy consisting of cyclophosphamide and adriamycine. She was 37 years old during her admittance for routine gynaecologic examination when she was on tamoxifen therapy and monthly goserelin injections for 18 months. She was amenorrheic for 15 months and was otherwise asymptomatic gynaecologically. Her gynaecologic examination was unremarkable except for a polypoid lesion of 1x0.5 cm on upper posterior vaginal wall. The lesion was removed under local anesthesia. On pathological examination, the lesion was composed of plump round, ovoid or spindle-shaped cells with eosinophilic cytoplasm, contained abundant capillary sized blood vessels (Figure 1). Alternating hypercellular and edematous hypocellular areas were noted in the tumor. Neoplastic cells were typically clustered around vessels within an edematous to collagenous matrix. Rarely binucleated cells were present. There was no nuclear atypia or mitosis. In immunohistochemistry, stromal cells were positive for desmin (Figure 2A), weakly positive for CD34, and negative for SMA (smooth muscle actin). Both estrogen and progesterone receptors were diffusely expressed (Figure 2B and 2C). The microscopic findings and immunohistochemical results were found to be consistent with angiomyofibroblastoma. No further therapy was planned due to the benign nature of the lesion. The patient was re-examined 10 months after polypectomy and was free of any signs or symptoms.

Basic characteristics of cases reported to have vaginal angiomyofibroblastoma were summarized in Table 1. Mean age of the patients including the present case was 58.8 years (range; 36-85 years). Among 9 patients with available data, the most common presenting symptom was a mass which was seen in 6 (66.7%) while 3 (33.3%) were asymptomatic. Interestingly, 5 patients (41.7%) had a personal history of breast cancer and 4 (33.3%) were given tamoxifen treatment with a mean duration of 4.1 months (range: 0.9-10 months). This finding might be valuable because histogenesis and etiopathogenesis of angiomyofibroblastoma have not been clearly identified yet. However, some authors think the neoplasm is probably derived from primitive mesenchymal cells of subepithelial myxoid stroma which may undergo differentiation to myofibroblasts under hormonal stimuli.

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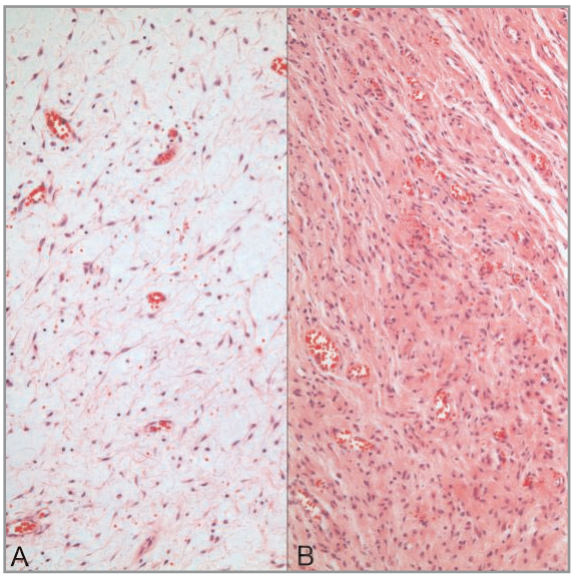

Figure 1. The tumor was characterized by alternating hypocellular (panel A) and hypercellular (panel B) areas (Hematoxylene-Eosin, x200).

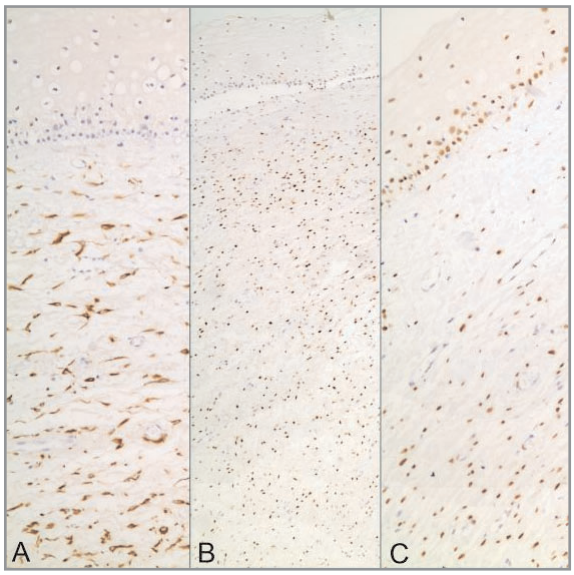

Figure 2. Neoplastic cells showed diffuse expression of desmin (panel A), progesterone receptor (panel B) and estrogen receptor (panel C) (A: Immunohistochemistry; Anti-desmin antibody, x200; B: Immunohistochemistry; Anti-progesterone receptor antibody, x100; C: Immunohistochemistry; Anti-estrogen receptor antibody, x200).

This assumption is consistent with findings of immunopositivity for vimentin, desmin, oestrogen and progesterone receptors.[10,12-14] In an attempt to clarify the indeterminate etiopathogenesis of this rare entity, some of the recently published articles suggested a possible relation between development of angiomyofibroblastoma and use of selective estrogen receptor modulators (SERMs).[3,7] Tamoxifen is the prototype of SERMs. It has clear anti-estrogenic effects on the breast and therefore is used orally for breast cancer treatment. However, due to its estrogenic effects, benign and malignant neop-

Table 1. Vaginal angiomyofibroblastoma cases reported in the English literature

Author and publication year	Age (years)	Clinical presentation	Tumor size (cm)	Breast cancer history	Use of tamoxifen
Nopdonrattakoon L, 2008[2]	36	Mass	10	No	No
Lee et al., 2008[3]	56	Protruding mass	2	Yes	Yes
Kumasaka et al., 2007[4]	74	Asymptomatic	NS*	Yes	NS*
Saleh et al., 2007[5]	62	Protruding mass	5	Yes	Yes
Faraj et al., 2007[6]	85	Protruding mass	10	No	No
Varras et al., 2006[7]	80	Protruding mass	6	Yes	Yes
Banerjee et al., 2004[8]	40	Mass	4	No	No
McCluggage et al., 2000[9]	54	Asymptomatic	2.5	No	No
Nielsen et al., 1996[10]	53	NS	0.9	No	No
	58	NS	1	No	No
	71	NS	2.6	No	No
Present case	37	Asymptomatic	1	Yes	Yes

*: not specified

Table 2. Vaginal angiomyofibroblastoma cases with a history of breast cancer

Author	Time of breast cancer diagnosis	Type and dose of SERM*	Ongoing SERM* treatment during diagnosis	Presence of ER** in vaginal tumor cells
Lee et al.[3]	4 years ago	Toremifene 40 mg/day	Yes	Yes
Kumasaka et al.[4]	19 years ago	NS***	NS***	Yes
Saleh et al.[5]	3 years ago	Tamoxifen Dose NS***	Yes	NS***
Varras et al.[7]	4 years ago	Tamoxifen 20 mg/day	Yes	Yes
Present case	2 years ago	Tamoxifen 20 mg/day	Yes	Yes

*: selective estrogen receptor modulator; **: estrogen receptor; ***: not specified

lastic changes may occur in genital organs including endometriosis, adenomyosis, leiomyomata, ovarian tumors, endometrial polyps, hyperplasia and carcinoma, and cervical polyps.[15] According to these findings, tamoxifen use is associated with higher than expected incidences of both epithelial and mesenchymal neoplasms of the female genital tract. Similarly, estrogenic effects of tamoxifen might trigger the differentiation of vaginal primitive mesenchymal cells into myofibroblasts which eventually leads to the development of angiomyofibroblastoma. First case supporting this assumption was reported by Varras et al. based on their experience of a vaginal angiomyofibroblastoma in a breast cancer patient who was treated with tamoxifen 20 mg/day for four years and was still on treatment during the diagnosis of vaginal tumor.[7] The case with a recurrent angiomyofibroblastoma of vagina published by Saleh et al.[5] was also on long-term tamoxifen therapy during the initial diagnosis. Although the patient reported by Kumasaka et al.[4] had a history of breast cancer and vaginal tumor was positive for estrogen receptor, nothing was mentioned about tamoxifen treatment in their report. Our present case was on tamoxifen treatment as well for 18 months at a daily dose of 20 mg during the diagnosis of vaginal angiomyofibroblastoma and estrogen receptors were detected to be expressed immunohistochemically within the neoplastic cells. In 2008, Lee et al.[3] reported another case of vaginal angiomyofibroblastoma which was detected in a woman who had a history of breast cancer and was treated with 40 mg/day oral toremifene for 3.5 years. Toremifene is a synthetic analogue of tamoxifen with fewer serious adverse effects.[16] The case published by Lee et al.[3] may indicate a similar association between toremifene treatment and the development of vaginal angiomyofibroblastoma. Table 2 summarizes some characteristics of vaginal angiomyofibroblastoma patients who had a personal history of breast cancer.

In conclusion, although very rare, angiomyofibroblastoma may occur in vagina and tamoxifen and similar drugs may lead to development of this neoplasm by exerting estrogenic effects upon mesenchymal cells of the female genital tissues. Therefore vaginal AMF should be considered as one of the lesions which may be detected as an adverse effect of treatment with tamoxifen or a similar drug.

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