Primary breast carcinoma of the vulva: Case report and review of literature

B. Piura[1], *M.D., F.R.C.O.G.*; **O. Gemer**[2], *M.D.* ; **A. Rabinovich**[1], *M.D.*; **I. Yanai-Inbar**[3], *M.D.*

[1]*Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, and* [3]*Institute of Pathology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev*

[2]*Department of Obstetrics and Gynecology, Barzilai Medical Center, Ashkelon, Affiliated to the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva (Israel)*

Summary

The occurrence of ectopic breast tissue within the vulva is uncommon and the development of breast carcinoma within vulvar ectopic breast tissue is very rare. To date, only 12 cases of primary vulvar breast carcinoma have previously been reported in the English literature. This paper presents the 13th reported case of primary breast carcinoma of the vulva. The patient presented with a vulvar ulcerated lump and the diagnosis was based on a morphologic pattern consistent with breast carcinoma and the presence of estrogen and progesterone receptors. Primary surgery consisted of radical vulvectomy and bilateral groin dissection. The groin lymph nodes were involved bilaterally. Adjuvant therapy consisted of systemic chemotherapy (4 cycles of adriamycin and cyclophosphamide followed by 4 cycles of paclitaxel) and pelvic radiotherapy. Oral tamoxifen 20 mg/day was started for the next five years. It is concluded that the management of primary breast carcinoma of the vulva should be modeled after that for primary carcinoma of the orthotopic breast with primary surgery followed by systemic chemotherapy and pelvic radiotherapy. Chemotherapy should be similar to that employed for breast carcinoma. Tamoxifen should be prescribed for patients whose tumors contain estrogen receptors.

Key words: Milk line; Ectopic breast; Vulvectomy; Groin dissection; Tamoxifen.

Introduction

In the five-week-old human fetus the ectodermal primitive milk streak (milk line, galactic band), extends from the axilla to the groin bilaterally. Incomplete regression of this streak may result in ectopic breast tissue developing anywhere along the milk line including the vulva. However, the occurrence of ectopic breast tissue within the vulva is rare with less than 50 cases documented in the literature [1-3]. Such ectopic breast tissue can be the site of the same physiologic and pathologic processes found in the normal orthotopic breast, including malignancy. However, the occurrence of primary breast carcinoma arising within ectopic breast tissue in the vulva is very rare with only 12 cases of primary vulvar breast carcinoma documented in the English literature [1-12]. This paper presents the 13th reported case of primary breast carcinoma of the vulva.

Case Report

A 69-year-old, gravida 9, para 9, postmenopausal Sephardic Jewish woman was referred in June 2000 because of a vulvar ulcerated and bleeding lump located on the left labium major of three-months' duration. There was no personal or family history of malignancy or breast disease. Physical examination disclosed an essentially healthy appearance and normal vital signs. The breast examination was unremarkable. Inspection of the external genitalia revealed a mobile, slightly tender, firm, bleeding, ulcerated 3 x 3 x 3 cm nodule located on the left labium major 1 cm from the clitoris. The lesion was not fixed to the underlying tissues and did not extend to the urethral meatus, vagina and anus. There was no Bartholin, Skene or vestibular gland abnormalities. Enlarged and fixed lymph nodes measuring 3 x 3 x 3 cm overall were palpated in the left groin, whereas no lymph nodes could be palpated in the right groin. Vaginal speculum examination revealed a normal-looking vagina and cervix. On bimanual pelvic examination the presence of normal internal genitalia was confirmed and no deep pelvic lymph nodes were palpable. An incisional biopsy of the vulvar lesion was interpreted as an adenocarcinoma with histological features consistent with apocrine (sweat) gland origin. A metastatic workup, including chest X-ray, bilateral mammography, computed tomography of the chest, abdomen and pelvis, isotopic bone scan, ultrasound examination of the abdomen, transvaginal ultrasound examination of the pelvis, and serum tumor markers (CA-15-3, CA-125, CA-19-9, CEA, AFP and beta-HCG), was unremarkable.

The patient underwent radical vulvectomy and bilateral groin dissection with use of the three-separate incision technique. The vulvar specimen, a large ellipse of skin and attached subcutaneous tissue, measuring 17 x 9 x 3 cm, contained the clitoris, labia majora and minora. In the anterior part of the left labium major was a 3-cm firm greyish-yellow mass with irregular borders. The mass eroded the skin. Histologic sections showed infiltrating ductal carcinoma with cribriform pattern (Figure 1). Small foci of intraductal carcinoma were also identified and some lymph vascular spaces were infiltrated by tumor cells. There was pagetoid involvement of the overlying epidermis with small groups of tumor cells. One of the lateral margins of the vulvectomy specimen was involved with a 3-mm focus of tumor, whereas the remaining margins were tumor-free. The tumor penetrated deeply into the subcutaneous tissue and the inferior margin of the specimen was close (2 mm) to the tumor. Immunohistochemical staining was positive for CA-15-3 and

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low molecular weight (L.M.W.) keratin, and weakly positive for high molecular weight (H.M.W.) keratin, chromogranin and gross cystic fluid disease protein-15 (GCFDP-15). Staining for estrogen receptor (ER) was strongly positive in 100% of tumor cells and staining for progesterone receptor (PR) was positive in 20% of tumor cells. Foci of ectopic lobular breast tissue were identified in the dermis adjacent to the tumor. The left groin specimen, a large piece of lymphatic fatty tissue and attached narrow strip of skin, measuring 14 x 8 x 4 cm, contained 6/7 positive lymph nodes. The right groin specimen, a large piece of lymphatic fatty tissue and attached narrow strip of skin, measuring 13 x 7 x 4 cm, contained 1/8 positive lymph nodes. Thus, 7/15 removed groin lymph nodes were positive overall, and the involvement was bilateral.

The patient made an uneventful postoperative recovery and was discharged home on the 15th postoperative day. She, however, developed a left groin lymphocyst which had to be drained by needle aspiration. A decision was made to treat her postoperatively in the same manner as for advanced-stage primary carcinoma of the orthotopic breast with systemic chemotherapy followed by radiotherapy. She received four cycles of intravenous chemotherapy with AC (adriamycin 60 mg/m^2 - day 1 and cyclophosphamide 600 mg/m^2 - day 1), at three-week intervals followed by four cycles of intravenous paclitaxel (taxol) 175 mg/m^2 - day 1, at three-week intervals. This was followed by external megavoltage photonic irradiation employing a 10 MeV linear accelerator delivering 5,040 cGy to the whole pelvis, groin and vulvar region, in daily fractions of 180 cGy via an AP-PA opposed fields. The patient was started on oral tamoxifen 20 mg per day for the next five years. To date, 14 months after diagnosis of primary breast carcinoma of the vulva and following extensive surgery, systemic chemotherapy, regional radiotherapy and initiation of oral tamoxifen, the patient is alive with no evidence of recurrent disease.

Discussion

During the fifth week of fetal life the two- to four-cell-layered ectodermal mammary streak, or milk line, or galactic band, extends onto the embryonic trunk from the axilla to groin bilaterally. Most of this streak disappears soon after its formation, but a small amount persists bilaterally in the thoracic region and thickens to form the mammary ridge, or primordium. The lactiferous ducts and alveoli of the normal human pair of orthotopic breasts develop from these primordia [1]. Incomplete regression of the mammary streak may result in aberrant mammary tissue occurring anywhere along the milk line including the vulva. However, the occurrence of ectopic breast tissue within the vulva has infrequently been encountered. Since the first report of a case of ectopic breast tissue arising within the vulva by Hartung in 1872, only less than 50 cases of ectopic vulvar breast tissue have been documented in the literature [1-3]. The diagnosis of ectopic vulvar breast tissue is based primarily on the characteristic histologic pattern of breast tissue. The presence of estrogen and progesterone receptors provides supporting evidence.

Aberrant breast tissue can be the site of the same physiologic and pathologic processes found in the normal orthotopic breast, including malignancy. However, the development of primary breast carcinoma within the vulva is very rare. In 1936, Green [4] was the first to describe a case of primary breast carcinoma of the vulva and only 13 cases of primary breast carcinoma of the vulva, including this case, have been documented in the English literature since that time [1-12, and this case] (Table 1). The patients' ages have varied from 46 to 71 years with the mean age (61 years) more consistent with that for breast cancer (62 years) rather than that for vulvar cancer (72 years). Of the 12 women in whom parity was recorded, three were nulliparous and nine had at least one child (range, 1 - 9 children). The mean parity of the parous women was 4.5 children. Presenting signs and symptoms have been similar to those seen with primary vulvar carcinoma and included vulvar mass or nodule (13 patients), ulceration (5 patients), bleeding (1 patient) and

Table 1. — *Cases of primary vulvar breast carcinoma documented in the literature.*

Year [Ref.]	Age (years)	Parity	Size and site of tumor	Surgery	Adjuvant therapy	Follow-up (months)
1936 [4]	49	G0P0	20x15 cm mass, Rt. Lab. Maj.	None	None	DOD (1)
1959 [5]	58	G7P7	3-cm nodule, Lt. Lab. Min.	RV	None	NA
1976 [6]	62	G8P5	1.5-cm nodule, Lt. Lab. Maj	WLE	None	DOD (24)
1984 [7]	49	G0P0	2-cm cyst, Lt. Lab. Maj.	RVBND	XRT	Alive (36)
1985 [8]	70	G0P0	3x4x4 cm nodule, Rt. Lab. Maj. ER/PR+	RHVIND	Tamoxifen	Alive (24)
1988 [9]	60	G2P2	2x2 cm nodule, Rt. Lab. Maj. ER/PR+	RVBND	Chemo/XRT, Tamoxifen	DOD (27)
1990 [10]	68	G2P2	3.5x3.5 cm mass, Rt. Lab. Maj. ER+	RVIND	XRT, Tamoxifen	NA
1992 [11]	46	NA	1.5-cm nodule, Rt. Lab. Maj.	RVBND	None	Alive (4)
1993 [3]	65	G3P3	3x2 cm lesion, Rt. Lab. Maj. ER/PR+	RVBND	Tamoxifen	Alive (12)
1995 [2]	62	G2P2	2.5-cm nodule, Lt. paraclitorial region	WLEIND	Tamoxifen	Alive (36)
1997 [12]	71	G8P8	5x2 mass, Lt. Lab. Maj.	RVBND	Chemo/XRT	Alive (15)
1999 [1]	64	G4P4	2.7x1 cm nodule, Lt. mons pubis	WLEIND	Chemo/XRT, Tamoxifen	Alive (4)
This case	69	G9P9	3x3x3 cm nodule, Lt. Lab. Maj.	RVBND	Chemo/XRT, Tamoxifen	Alive (12)

Abbreviations: G=gravidity; P=parity; Rt=right; Lt=left; Lab=labium; Maj=major; Min=minor; ER=estrogen receptor; PR=progesterone receptor; RV=radical vulvectomy; RHV=radical hemivulvectomy; WLE=wide local excision; BND=bilateral groin lymph node dissection; IND=ipsilateral groin lymph node dissection; XRT=radiotherapy; Chemo=chemotherapy; DOD=dead of disease; NA=not available.

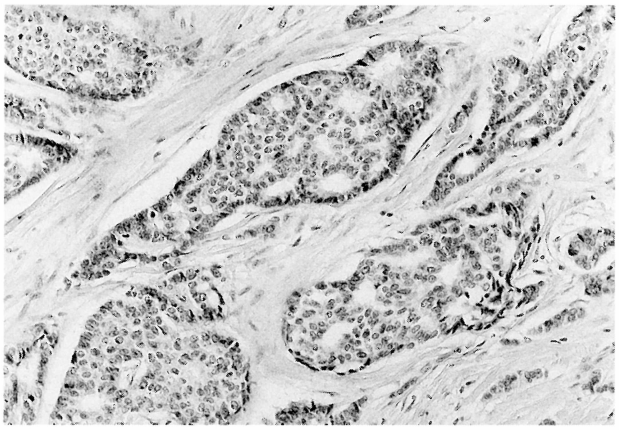

Figure 1. - Primary breast carcinoma of the vulva. Infiltrating ductal carcinoma with cribriform pattern (H&E x 200).

pain (1 patient). The duration of symptoms has also been similar to that seen with primary vulvar carcinoma, varying anywhere from a few months to several years. Size (largest diameter) of the tumor ranged from 1.5 cm to 20 cm (mean, 4 cm). In most of the patients the tumor was mobile and not fixed to the underlying tissues. The tumor was located on the right labium major (6 patients), left labium major (4 patients), left labium minor (1 patient), mons pubis (1 patient) and clitoris (1 patient). Data with respect to both clinical palpation and histopathologic examination of groin lymph nodes was available in nine patients. Clinical palpation detected palpable nodes (clinically positive nodes) in six patients and failed to detect palpable nodes (clinically negative nodes) in three patients. In all six patients who had clinically positive nodes, histopathologic examination detected lymph node metastases (positive predictive value of clinical palpation, 100%). In all three patients who had clinically negative nodes, histopathologic examination detected lymph node metastases (negative predictive value of clinical palpation, 0%). The sensitivity (detection rate) and specificity of clinical palpation as a test for detecting groin lymph node metastases was 66.6% and 0%, respectively.

The diagnosis of primary breast carcinoma arising in the vulva is based on the following histologic criteria [1]: (1) a morphologic pattern consistent with breast carcinoma, (2) the presence of estrogen and progesterone receptors, and/or (3) positivity for common breast cancer markers such as CA-15-3, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), gross cystic fluid disease protein-15 (GCFDP-15) and glandular keratins. Diagnosis is initially made by biopsy of the vulvar lesion and thereafter confirmed by surgery. The differential diagnosis of primary vulvar breast carcinoma includes metastatic breast carcinoma, adenocarcinomas of skin appendages (apocrine or sweat gland adenocarcinoma), and lesions associated with extramammary Paget's disease of the vulva. In this patient, biopsy of the lesion was interpreted as adenocarcinoma with histologic features consistent with apocrine (sweat) gland origin. However, histologic examination of the vulvectomy and the groin dissection specimens showed that the tumor was a primary breast carcinoma of the vulva metastasizing to the groin lymph nodes. The presence of estrogen and progesterone receptors provided supporting evidence.

When breast carcinoma arising within the vulva is diagnosed, a thorough metastatic workup is mandatory with special attention directed toward detecting a primary carcinoma of the orthotopic breast by history, physical examination, and radiologic examination of the breasts. Of the 13 patients with primary vulvar breast carcinoma documented in the literature, two had primary carcinoma of the orthotopic breast occurring either metachronously or synchronously with primary vulvar breast carcinoma [6, 12]. Kennedy et al [12] have described a 71-year-old patient who had an infiltrating ductal carcinoma of the left breast occurring four years before the detection of primary breast carcinoma of the vulva. Guerry and Pratt-Thomas [6] have reported the case of a 62-year-old patient who in addition to primary vulvar breast carcinoma had two primary breast carcinomas: (1) intraductal and infiltrating scirrhous duct carcinoma of the right breast occurring five and one half years before the detection of primary vulvar breast carcinoma; and (2) intraductal and infiltrating carcinoma of the left breast detected concomitantly with primary vulvar breast carcinoma.

The rarity of primary breast carcinoma of the vulva has made assessment of the most effective management difficult [1-3]. In the 13 patients whose cases have been documented in the literature, the primary treatment employed most often has been surgical. One patient had no surgery [4], one patient had wide local excision of the vulvar tumor only [6], two patients had wide local excision of the vulvar tumor with ipsilateral inguinofemoral lymphadenectomy [1, 2], one patient had radical vulvectomy only [5], and the remaining eight patients had radical vulvectomy with either ipsilateral or bilateral inguinofermoral lymphadenectomy [3, 7-12, and this case]. Seven patients did not receive adjuvant chemotherapy or radiotherapy [2-6, 8, 11], two patients received adjuvant therapy with pelvic radiotherapy alone [7, 10], and four patients received adjuvant intravenous chemotherapy followed by pelvic radiotherapy [1, 9, 12, and this case]. Of the four patients who received adjuvant chemotherapy, one patient received five cycles of CAF (cyclophosphamide, adriamycin, and 5-fluorouracil) [9], one patient received six cycles of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) [1], one patient received three cycles of AC (adriamycin and cyclophosphamide) [12], and one patient received four cycles of AC followed by four cycles of paclitaxel (taxol) [this case]. In patients who had radiotherapy, it consisted of a total dose ranging from 4,500 cGy to 5,040 cGy given to the whole pelvis, groin and vulva [1, 7, 9, 10, 12, and this case]. Seven patients (of whom, five had a tumor staining positively for estrogen receptors) were started on oral tamoxifen 20 mg/day after primary surgery and adjuvant therapy [1-3, 8-10, and this case]. It has generally

been agreed upon that the treatment of primary breast carcinoma of the vulva should be modeled after that for primary carcinoma of the orthotopic breast with primary surgery followed by adjuvant therapy being the mainstay of treatment [1-3]. It has been emphasized that since breast carcinoma is currently treated as a systemic disease with primary surgical excision of the tumor and axillary lymph node dissection, followed by varying combinations of systemic chemotherapy, radiation therapy, and/or hormonal therapy, we must look to the current management of breast carcinoma in order to establish a sensible approach for the management of primary breast carcinoma of the vulva [1,3]. It has also been concluded that a five-year course of tamoxifen 20 mg/day should be given to patients with primary vulvar breast carcinoma containing estrogen receptors [3].

Follow-up of the 13 patients ranged from one to 36 months, with six patients followed for at least two years or until time of death. At the end of follow-up, eight patients were alive and free of disease, three had died of disease and two were lost to follow-up. It is difficult to draw conclusions about the prognosis of patients with primary vulvar breast carcinoma from such a small number of patients and such a short follow-up period. However, since most patients with primary vulvar breast carcinoma have groin lymph node metastases at the time of diagnosis, it is reasonable to assume that (1) there is a considerable delay in the diagnosis of this disease and (2) the prognosis of patients with primary vulvar breast carcinoma is worse than that of patients with primary carcinoma of the orthotopic breast.

Conclusion

Primary breast carcinoma of the vulva is very rare with only 13 documented cases in the English literature. The differential diagnosis of primary vulvar breast carcinoma includes metastatic breast carcinoma, primary vulvar apocrine (sweat) gland carcinoma, invasive vulvar extramammary Paget's disease, and primary vulvar carcinoma of the major and minor vestibular glands. The diagnosis of primary breast carcinoma of the vulva is based on a morphologic pattern consistent with breast carcinoma, presence of estrogen and progesterone receptors and absence of primary adenocarcinoma elsewhere metastasizing to the vulva. Treatment is modeled after that for primary carcinoma of the orthotopic breast with primary surgery including excision of the tumor with wide margins (most often radical vulvectomy) and groin dissection (most often bilateral) followed by systemic chemotherapy and pelvic radiotherapy. Chemotherapy should be identical to that used for breast carcinoma. Tamoxifen should be prescribed for patients with tumors containing estrogen receptors. It seems that primary vulvar breast carcinoma tends to metastasize early and the prognosis is worse than that of primary carcinoma of the orthotopic breast.

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Address reprint request to:
B. PIURA, M.D., F.R.C.O.G.
Unit of Gynecologic Oncology
Department of Obstetrics and Gynecology
Soroka Medical Center
and Faculty of Health Sciences
Ben-Gurion University of the Negev,
P.O.Box 151,
84101 Beer-Sheva (Israel)