

Breast-like cancer of the vulva: primary or metastatic?

A case report and review of the literature

D. Miliaras¹, M.D., Lecturer

Pathology Department, General Clinic, Thessaloniki,
and ¹Laboratory of Histology and Embryology,
Medical Faculty, Aristotelian University of Thessaloniki (Greece)

Summary

A 45-year-old white female presented a polypoid nodule in the vulva, one year after she was operated on for breast cancer. Histologic examination showed a poorly differentiated carcinoma that closely resembled the primary breast tumor. Eight similar cases have been previously described in the literature. This very rare event should be differentiated from primary adenocarcinoma of the mammary-like glands of the vulva. The recognition of such a lesion as primary or metastatic is very important, since it greatly influences management and prognosis.

Key words: Breast carcinoma; Vulva; Metastasis; Mammary-like glands.

Introduction

Breast carcinoma is the most common malignant tumor and the leading cause of cancer death in females [1]. Metastases from mammary carcinoma may be seen at virtually any site, but most common are the lymph nodes, bones, lungs and pleura, adrenal glands, liver and the central nervous system [2]. The female genital tract may also be involved by metastatic disease, more frequently affecting the ovary and more rarely the endometrium and the vagina [3]. The vulva is one of the more unusual sites of metastases from breast carcinoma, with only eight cases published in the literature [4-11]. One more similar event is reported in this paper. Meanwhile, 14 cases of primary breast cancer of the vulvar region have also been described [12-18]. Differentiation between primary and secondary breast carcinoma of the vulva is not always an easy task. Adherence to strict criteria is needed for correct interpretation of a case presenting with a breast-like invasive carcinoma in this region.

Case Report

This case concerns a 45-year-old white female. She had already been subjected to right mastectomy and axillary node dissection for breast cancer. The original breast tumor measured 3 cm in diameter. Histology revealed invasive ductal carcinoma, not otherwise specified, grade III according to the Bloom & Richardson criteria. Four out of the 14 axillary lymph nodes had focal to widespread metastases from the same tumor. Estrogen and progesterone receptors were negative. The initial evaluation of the patient showed no evidence of distant metastases, thus the patient was treated with systemic chemotherapy for 12 months (cyclophosphamide: 100 mg/m² p.o., methotrexate 40 mg/m² i.v., 5-fluoracil 600 mg/m² IV). One year after the operation, she presented a solitary, exophytic, polypoid nodule in the right labia majora, 1 cm in diameter. The gynaecologist initially

thought this might be a condyloma acuminatum, and so he cauterised it. However, the lesion recurred a few weeks later and surgical excision was performed. After four months the patient developed bone metastases and died 11 months after the removal of the vulvar lesion.

Pathological findings

The surgical specimen consisted of a skin nodule that measured 2 cm in diameter. Routine histologic examination (10% buffered neutral formalin fixation, paraffin embedding and hematoxylin & eosin staining) showed an invasive carcinoma (Figure 1). The neoplastic cells formed solid nests and presented significant nuclear atypia, prominent nucleoli and many

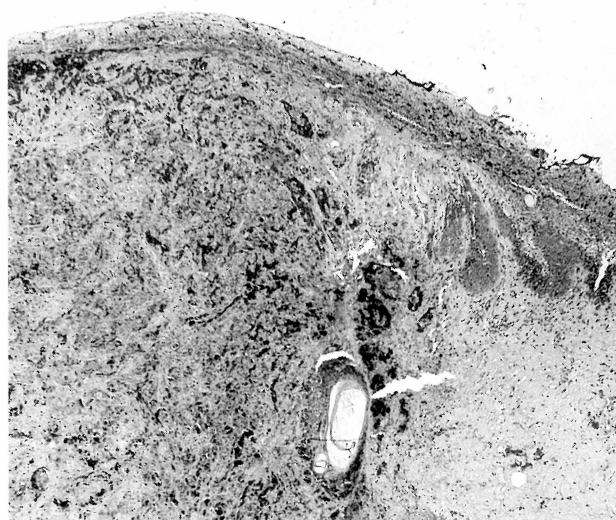


Figure 1. — Widespread infiltration of the dermis from poorly differentiated carcinoma. The rete ridges of the adjacent epidermis are elongated but they do not show changes of in situ carcinoma (H&E, x50).

Revised manuscript accepted for publication January 22, 2002

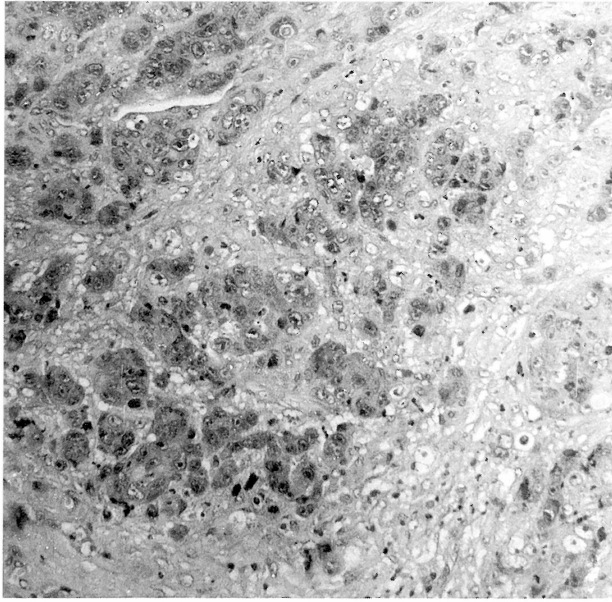


Figure 2. — Higher magnification of the vulvar lesion, showing solid nests of neoplastic cells with marked nuclear atypia and many mitoses (H&E, x200).

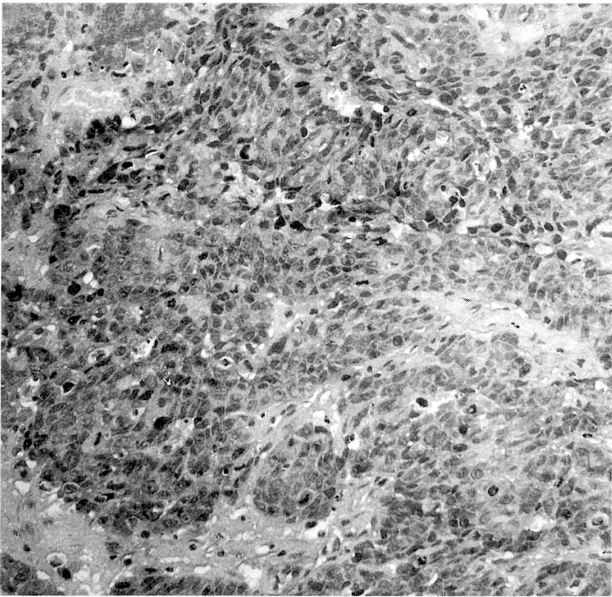


Figure 3. — The original breast tumor from the same patient closely resembles the vulvar lesion (H&E, x200).

mitoses (Figure 2). The overlying skin was ulcerated, but the adjacent epidermis did not present any significant changes. The lesion grew with expansile borders. An intense desmoplastic reaction was observed in the intervening stroma. The neoplasm had similar microscopic features with the primary breast tumor (Figure 3). The diagnosis was poorly differentiated carcinoma, consistent with metastatic ductal breast carcinoma. Immunohistochemical detection of p53 protein, estrogen and progesterone receptors (all Novocastra, U.K.), using a streptavidin-biotin method, were negative.

Discussion

Not all organs and tissues are equally susceptible to the development of metastases. For example, spleen and skeletal muscle are relatively uncommon sites of metastasis, while the ovaries, the liver and the lungs are frequent and sometimes preferential locations of tumor metastasis. These differences in the “soil” are not well understood and may be related to such factors as variation in vascular size and permeability, local nourishment and local resistance. In a large series of patients with metastases to the female genital tract from extragenital tumors, Mazur *et al.* found that the vulva was the second most uncommon site of metastasis, the ovary being the commonest and the salpinx the rarest [3]. The literature suggests that metastasis of breast carcinoma to the vulva is also a very rare event [4-11].

The clinical significance of breast cancer metastasis to the vulva is that these lesions, although infrequent, may be confused with primary tumors. Sometimes metastatic tumors may be discovered before the breast primaries, making the possibility of an erroneous diagnosis of vulvar carcinoma more likely. Carcinomas arising from supernumerary mammary tissue derived from remnants of the milk ridges in the vulva especially have similar histologic features with carcinoma of the breast. These adenocarcinomas of supernumerary mammary tissue may be positive for estrogen and progesterone receptors [11, 12, 16, 17]. The current data support the view that lesions attributed to the so-called supernumerary mammary tissue of the vulva mostly arise from mammary-like glands of the vulva which are closely linked to eccrine glands [19]. However, in extremely rare cases true vulvar breast with nipple and ectopic mammary tissue may also occur.

Features favouring that a breast-like carcinoma of the vulva is metastatic are multifocality, presence of tumor emboli in vessels, and histologic resemblance of the lesion with a known primary tumor of the breast. On the other hand, absence of primary breast tumor, presence of mammary-like glands in the vicinity of the tumor, in situ carcinoma or dysplastic changes in the adjacent glands or covering epithelium of the vulva, support a diagnosis of primary vulvar carcinoma. However, differential diagnosis is not straight-forward in every case. Multifocality (multiple foci of the same tumor), multicentricity (multiple independent tumors), and bilaterality, are all well-recognized, and frequent phenomena that characterize breast cancer [20, 21]. This multifocal activation of mammary epithelium may be due to a field defect from underlying genomic instability, and could involve mammary tissue in any site. Accordingly, certain cases of metastatic breast cancer to the vulva described in the literature may also be interpreted in a different manner. When a vulvar breast-like carcinoma arises after a very long interval from the primary breast tumor for example (14 years later in the case of Porzio *et al.* [11]), without evidence of metastases to any other organ in the course of the disease, the vulvar lesion would rather be regarded as a second primary. Likewise, when two tumors arise in

the vulva and the breast simultaneously (as in case of Menzin *et al.* [10]), it is more conceivable that these lesions represent independent synchronous neoplasms rather than the one being primary and the other metastatic, if no metastases in any other site are found. In my opinion, we should be very reluctant to diagnose the vulva as the sole site of metastasis of breast carcinoma. In our case, the clinician initially thought that the vulvar tumor represented a local benign lesion. However, it proved to be a carcinoma, histologically resembling the patient's own breast cancer. There were neither mammary-like glands in the vicinity of the lesion nor any dysplastic changes in the adjacent covering epithelium of the vulva. The patient already had a T2, N2-stage disease. Development of widespread bone metastases a few months later also supports a diagnosis of metastatic vulvar tumor after a breast primary.

Molecular analysis by means of oligonucleotide microarrays [22], methylation-specific polymerase chain reaction [23], microsatellite analysis for loss of heterozygosity [24], etc., could be of value in order to clarify equivocal cases. However, genetic heterogeneity does not always imply a multicentric origin in breast cancer. Cytogenetic investigations have shown that polyclonality is an inherent feature of breast cancer [25]. Single breast tumors frequently present different chromosome abnormalities in different areas of the same lesion [26]. In addition, comparisons between breast carcinomas and their lymph node metastases have shown that polyclonality may exist in both the primary and the secondary tumor [27]. In conclusion, all available clinical, pathological, and molecular data should be carefully evaluated when facing such diagnostic dilemmas (i.e. primary tumor vs metastatic). The recognition of a vulvar lesion as metastatic is very important in terms of therapy and prognosis, since this usually consists of an ominous prognostic sign as our case characteristically illustrates.

References

- [1] Parker S. L., Tong T., Bolden S., Wingo P. A.: "Cancer Statistics, 1997". *CA Cancer J. Clin.*, 1997, 47, 5.
- [2] Cifuentes N., Pickren J. W.: "Metastases from carcinoma of mammary gland. An autopsy study". *J. Surg. Oncol.*, 1979, 11, 193.
- [3] Mazur T., Hsueh S., Gersell D. J.: "Metastases to the female genital tract: Analysis of 325 cases". 1978, *Cancer*, 1984, 53, 1978.
- [4] Convington E. E., Brendle W. K.: "Breast carcinoma with vulvar metastases". *Obstet. Gynecol.*, 1964, 23, 910.
- [5] Dehner L. P.: "Metastatic and secondary tumors of the vulva". *Obstet. Gynecol.*, 1973, 42, 47.
- [6] Mader M. H., Friedrich E. G.: "Vulvar metastasis of breast carcinoma: a case report". *J. Reprod. Med.*, 1982, 2, 169.
- [7] Cohen R., Margolius K. A., Guidozzi F.: "Non-gynaecological metastases to the vulva and vagina". *S. Afr. Med. J.*, 1988, 73, 159.
- [8] Patsner B.: "Bartholin's gland metastases from breast cancer: a case report". *Eur. J. Gynaecol. Oncol.*, 1996, 17, 96.
- [9] Curtin W. M., Murthy B.: "Vulvar metastasis of breast carcinoma. A case report". *J. Reprod. Med.*, 1997, 42, 61.
- [10] Menzin A. W., De Risi D., Smilari T. F., Kalish P. E., Vinciguerra V.: "Lobular breast carcinoma metastatic to the vulva: a case report and literature review". *Gynecol. Oncol.*, 1998, 69, 84.
- [11] Porzio G., Ficorella C., Calvisi G., Paris I., Ricevuto E., Marchetti P.: "Ductal breast carcinoma metastatic to the vulva: a case report". *Eur. J. Gynaecol. Oncol.*, 2001, 22, 147.
- [12] Cho D., Buscema J., Rosenhein N.B., Woodruff J.D.: "Primary breast cancer of the vulva". *Obstet. Gynecol.*, 1985, 66 (3 Suppl), 79S.
- [13] Simon K. E., Dutcher J. P., Runowicz C. D., Wiernik P. H.: "Adenocarcinoma arising in vulvar breast tissue". *Cancer*, 1988, 62, 2234.
- [14] Levin M., Pakarakas R. M., Chang H. A., Maiman M., Goldberg S. L.: "Primary breast carcinoma of the vulva: a case report and review of the literature". *Gynecol. Oncol.*, 1995, 56, 448.
- [15] Kennedy D. A., Hermina M. S., Xanos E. T., Schink J. C., Hafez G. R.: "Infiltrating ductal carcinoma of the vulva". *Pathol. Res. Pract.*, 1997, 193, 723.
- [16] Irvin W. P., Cathro H. P., Grosh W. W., Rice L. W., Andersen W. A.: "Primary breast carcinoma of the vulva: a case report and literature review". *Gynecol. Oncol.*, 1999, 73, 155.
- [17] Neumann I., Strauss H. G., Buchmann J., Koelbl H.: "Ectopic lobular breast cancer of the vulva". *Anticancer Res.*, 2000, 20, 4805.
- [18] Gorisek B., Zegura B., Kavalar R., But I., Krajnc I.: "Primary breast cancer of the vulva: a case report and review of the literature". *Wien Klin. Wochenschr.*, 2000, 112, 855.
- [19] Van der Putte S. J. C.: "Mammary-like glands of the vulva and their disorders". *Int. J. Gynecol. Pathol.*, 1994, 13, 150.
- [20] Luttes J., Kalbfleisch H., Prinz P.: "Nipple involvement and multicentricity in breast cancer. A study on whole organ sections". *J. Cancer Res. Clin. Oncol.*, 1987, 113, 481.
- [21] Holland R., Veling S. H., Mravunac M., Hendriks J. H.: "Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery". *Cancer*, 1985, 56, 979.
- [22] Unger M. A., Rishi M., Clemmer V. B., Hartman J. L., Keiper E. A., Greshock J. D. *et al.*: "Characterization of adjacent breast tumors using oligonucleotide microarrays". *Breast Cancer Res.*, 2001, 3, 336.
- [23] Kim N. G., Roh J. K., Kim J. H., Chung W. Y., Park C. S., Kim H.: "Clonality analysis using methylation-specific polymerase chain reaction: a novel method for investigating tumor clonality". *Lab. Invest.*, 1999, 79, 1727.
- [24] Zhang L., Epstein J., Band P., Berean K., Hay J., Cheng X., Rosin M. P.: "Local tumor recurrence or emergence of a new primary lesion? A molecular analysis". *J. Oral Pathol. Med.*, 1999, 28, 381.
- [25] Heim S., Teixeira M. R., Dietrich C. U., Pandis N.: "Cytogenetic polyclonality in tumors of the breast". *Cancer Genet. Cytogenet.*, 1997, 95, 16.
- [26] Teixeira M. R., Pandis N., Bardi G., Andersen J. A., Heim S.: "Karyotypic comparisons of multiple tumorous and macroscopically normal surrounding tissue samples from patients with breast cancer". *Cancer Res.*, 1996, 56, 855.
- [27] Pandis N., Teixeira M. R., Adeyinka A., Rizou H., Bardi G., Mertens F. *et al.*: "Cytogenetic comparison of primary tumors and lymph node metastases in breast cancer patients". *Genes Chromosomes Cancer*, 1998, 22, 122.

Address reprint requests to:
D. MILIARAS, M.D.
75 Tsimiski Street,
GR54622 Thessaloniki (Greece)