Metastases to the breast from melanoma: a rare manifestation of an unpredictable malignant disease

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Cancer metastases to the breast are not frequent. The most common among them are those originating from melanoma.

The course of this disease is often unpredictable, but the changes in the menstrual status may in some patients induce local changes in the breast that facilitate the growth of melanoma metastases. These changes are probably caused by physiological changes in serum estrogen levels, with the causes behind trafficking of melanoma cells to the breast remaining unclear. Patients with melanoma metastases to the breast will be encountered more frequently, as the incidence rate of melanoma increases worldwide.

These metastases usually manifest themselves as palpable mobile masses. Mammographic findings are of one or more rounded, well-circumscribed lesions with slightly irregular margins. The palpable and the mammographic dimensions of these lesions are usually closely correlated. Fine needle aspiration cytology of described lesions is a quick, safe and highly accurate diagnostic procedure.

Surgical excision is the appropriate treatment that provides local control with or without adjunctive chemo- and immunotherapy. Although mastectomy has not improved survival, it is sometimes required if the tumor is bulky, deep-seated, or painful.

Key words: breast-neoplasms-secondary; melanoma, melanoma-secondary; carcinoma-diagnosis; carcinoma-treatment

Introduction

Cancer metastases to the breast are not frequent, with the exception of those from contralateral breast.[1] They represent 2.7 % of all malignant breast tumors.[2] In a series of women treated for breast tumors, less than 1 % had metastases to the mammary gland from other primaries,[3,4,5] whereas in autopsy studies the overall frequency of cancer metastases to the breast ranged between 1.7 and 6.6 %.[3,6]

Melanomas are among the most common primary sites.[1,4,5,7-11] As the incidence of melanoma is increasing all over the world,[12-14] and as approxi-

mately 20 % of patients will eventually develop metastases,[15] an increase in the incidence of melanoma metastases to the breast can be expected.

It is surprising that melanoma which originates in the skin and disseminates widely throughout the body, often predominantly in the skin, rarely metastasizes to the parenchyma of the breast which is a skin appendage.[11]

Natural history of disease

Rapid growth is an important characteristic of cancer metastases in the breast.[1,16] Furthermore, cancer metastases to the breast are generally a harbinger of wide dissemination and fulminant course of the disease. Such patients thus show very short survival, usually less than 1 year.[1,5,9,17,18]

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The nature of malignant melanoma is often unpredictable and no other tumor is considered so capricious in its dissemination.[11] No clear predisposing factors correlating with the development of melanoma metastases to the breast have been identified.[9] It is not clear, whether hormonal factors have any influence on the natural history of the disease. On the other hand, some reports suggest that the changes in the menstrual status may induce some local changes in the breast that facilitate the growth of the melanoma metastases situated there.[17,18] These changes are probably caused by physiological changes in serum estrogen levels.

It is interesting to note that estrogen therapy for advanced carcinoma of the prostate may also cause the growth of metastases in the breast and nipple.[19,20] Some data suggest that changes in hormonal factors correlate with the development of breast metastases in males with various cancers[4] and in young females with rhabdomyosarcoma.[21]

However, it was reported that the patients with melanoma metastases to the breast were mostly premenopausal women and some of them were pregnant.[4,17,18] Together with the data that low levels of estrogen receptors have been sometimes observed on melanoma cells,[22-24] these reports additionally suggest that there may be some hormonal influence involved in the trafficking of melanoma cells to the breast as well.

The role of estrogens and other hormones in the natural history of melanoma remains controversial. Extremely poor prognosis was reported for patients with melanoma developed during pregnancy[25] and in postmenopausal period.[26,27] On the other hand, some recent studies show that pregnancy does not activate cutaneous melanoma or latent melanoma metastases as well.[28,29] Possible adverse or beneficial effects of oral contraceptives, estrogen and progesterone on the history of melanoma were evaluated,[22,30-32] but the results of clinical trials with hormone therapy were disappointing.[23,24,33] Additionally, it seems that the better prognosis of females with melanoma, especially of premenopausal patients,[26,34] cannot simply be explained by the presence of steroids receptors, since they were found in male patients as well.[22]

A higher proportion of thin melanoma lesions in women may contribute to an overall better prognosis for them. Nevertheless, survival rates for women were still higher than for men, even when primary lesions were of similar thickness. But, when premenopausal women were matched with men by age and location and thickness of primary lesion, a marked female superiority still exists only for those patients with very thick lesions.[27]

Despite the fact that patients with melanoma metastases to the breast are mostly premenopausal women, their prognosis remains poor. There seems to be a certain barrier against metastatic dissemination in premenopausal women,[35] but it seems it is no more effective when melanoma metastases to the breast are observed in these patients.

The occurrence of melanoma in children is uncommon.[14,36] In the report on a 14-year-old girl with melanoma metastases to the breast and brain there is no record about her menstrual status.[36] It can be presumed that her pubertal period was connected with changes in her hormonal status that may have had some influence on the course of the disease. But, the rarity of melanoma before puberty may simply reflect absence of a carcinogenic stimulus and a long latent period.

Long median intervals between the initial diagnosis of primary melanoma and involvement of breast have usually been observed[3,18] and the longest interval of 11 years was registered in a patient who was pregnant at the time of diagnosis.[18]

The most common primary sites of melanoma associated with breast involvement are on the arms and trunk. This is contrary to the most common sites in premenopausal women, namely the lower extremities. There my be a direct lymphatic and vascular drainage from these sites to the breast and this can be regarded as one of the factors that influence the natural course of this disease.[18,27,37]

The factors behind the occurrence of the melanoma metastases to the breast remain more or less unclear, but it is possible that patients with this type of metastatic dissemination will be seen more frequency as the incidence of melanoma increases worldwide.[12,13]
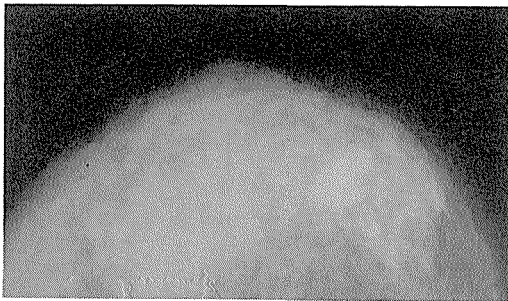
Diagnosis

Most patients have a known diagnosis of carcinoma at the time of presentation with breast metastases.[9,16,17] Occasionally, a breast metastasis is the first manifestation of an occult primary lesion.[1,3,4,9,38,39]

Metastases to the breast usually manifest themselves as palpable mobile breast masses that are sometimes adherent to the skin.[1,5] Diffuse skin involvement or associated subcutaneous nodules can also occur.[8] The metastases may be multiple and

can be observed in both breasts.[3,5] Tumor dimensions do not help to distinguish between primary and metastatic cancer. Although it is claimed that metastases are usually smaller than primary tumors, metastases may eventually become huge in size.[39]

The classic mammographic finding (Figure 1) consists of one or more rounded, well-circumscribed masses with slightly irregular margins.[9,16,40,41] Microcalcifications are unusual,[8,9] but it should be stressed that the presence of microcalcifications does not rule out a metastasis.[19] Since a metastatic lesion does not cause a surrounding desmoplastic reaction in adjacent normal breast, there is typically a close correlation between the palpable size of the mass and its mammographic size.[1,9,16] However, the same size seen in clinical examination of breast metastases and mammography could lead to a difficult differential diagnosis with benign breast lesions such as cysts or fibroadenomas. This contrasts with primary carcinoma of the breast, in which the mammographic abnormality is often smaller than the palpable mass.
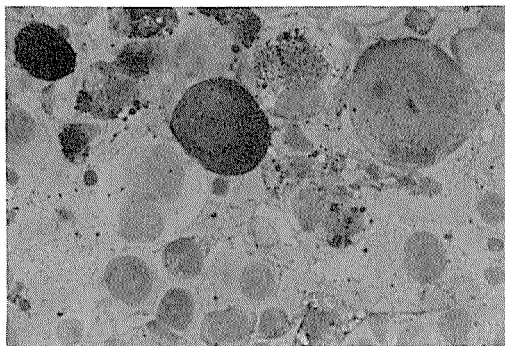
In young women ultrasound examination of breast should be done. We can usually see metastases to the breast as hypoechogenic nodules of different sizes, with regular margins and posterior attenuation of the posterior ultrasound beam.[40]

Particularly when the clinical evaluation is suggestive of metastatic disease, diagnostic fine needle aspiration biopsy may be confirmatory (Figure 2 and 3). The cell pattern in metastases of melanoma is generally pleomorphic.[44] Special stains (HMB45, S100, Warthin Starry)[18,44,45] and electron microscopy may be applied to this material as well to provide additional diagnostic information. Due to high diagnostic accuracy, fine needle aspiration cytology should be routinely practised as a quick and safe diagnostic procedure. It should be a very reliable method of distinguishing primary carcinoma from metastatic melanoma. Sometimes ultrasound guided and stereotactic fine needle aspiration biopsy should be applied if metastatic lesion is very small and not palpable.

Figure 1. Patient with melanoma metastasis to the breast. Craniocaudale view of the left breast reveals two well-defined masses.

Figure 2. Fine needle aspirate of melanoma metastasis to the breast – epytheloid type (Giemsa, objective 40).
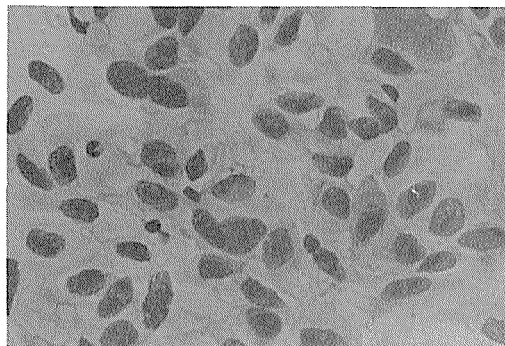
There is no doubt that mammography is the primary method to image breast tissue and evaluate specific breast lesions. As a primary technique for breast imaging, computed tomography (CT) compares poorly to mammography.[42] But, on occasion, breast lesions may be better visualized by CT than by mammography if the breasts are dense, or if the lesion is located adjacent to the chest wall.[43] The superb contrast resolution of CT allows a characterization of the density of the breast lesion and may augment the diagnostic possibilities. However, in most cases a recognition of a CT abnormality of the breast suggests the need for mammographic correlation.[42]

Figure 3. Fine needle aspirate of melanoma metastasis to the breast – fusocellular type (Giemsa, objective 40).

Open biopsy is rarely required for diagnosis if a primary breast tumor is not confirmed by the fine needle aspiration biopsy.[9,16,19,46-48] Until some years ago, the most helpful finding for identifying a metastatic malignancy in the breast was the recognition of the architectural pattern of the tumor, such as the presence of periductal infiltration without the coexistence of intraductal or intralobular carcinoma. But recently, immunohistochemistry has been suggested to differentiate metastatic carcinoma from a primary breast tumor in surgical specimens, and to avoid unnecessary radical surgery.[10,19] Further reports stress the importance of using a panel of immunohistochemical markers. For melanoma this should include at least two epithelial markers (i.e. BRST2, Human milk fat globulin 2 – HMFG2, CAM 5.2)[38,49] and at least two antibodies to melanoma-associated antigens (i.e. HMB45, S-100, NK1-C3).[38,50]

Occasionally, patients with breast metastases from melanoma were initially misdiagnosed.[4] Therefore for patients with a previous history of melanoma, however remote, the diagnosis of breast metastases in a premenopausal woman must be considered.[18]

Treatment

Accurate diagnosis of breast metastasis is important for avoiding unnecessary mastectomy and for implementing appropriate systemic therapy – since the metastatic disease is generally present at other sites as well.[1,3,16,51] This is particularly important if the lesion is the first sign of an extramammary malignancy.[9]

Excisional biopsy is usually the appropriate treatment and provides adequate local control with or without adjunctive chemo- and immunotherapy.[9,11,16,52] Conservative excision is recommended since mastectomy has not improved survival of patients with melanoma metastases to the breast.[11] Simple mastectomy is sometimes required if the tumor is bulky, deep-seated, or painful. Radical surgery should mostly be avoided unless needed for palliation.[1,3,5,16,17] In patients with terminal stage of disseminated melanoma, the best supportive care is mandatory.

There are no data as to in how many patients with melanoma breast metastases the axillary lymph nodes are involved. The involvement of axillary lymph nodes in patients with breast metastases from all

extramammary malignancies taken together is not so rare. It was observed in about 14 % to 42 % of them, most frequently in those with lymphomas.[53,54]

In addition to surgical treatment, adequate systemic therapy for the melanoma should be instituted9 when possible in clinical trials. Although the response rate of breast metastases to systemic therapy is similar to that of other sites, the finding of breast metastases is regarded as a poor prognostic sign.[18]

The overall prognosis for patients with metastatic melanoma to the breast is poor with more than 80 % dying within one year.[5,9,16]

Acknowledgments

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