

C A S E R E P O R T

Breast metastasis in a young pregnant woman affected by metastatic melanoma

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Abstract. Metastasis to the breast from extramammary tumors are rare, and the most common cancer that metastasizes to this site is malignant melanoma (MM). Unfortunately, metastases from malignant melanoma reveal a widespread of the disease and a high likeliness of poor diagnosis. In this study, a case of left breast metastasis of MM in a young pregnant woman, with a fast progression of the mammary and systemic course of pathology and unfortunately poor prognosis is presented. Despite the role of pregnancy in MM has yet to be unraveled, our study encourages the theory that immunosuppression and hormonal changes due to pregnancy may aggravate melanoma prognosis. (www.actabiomedica.it)

Key words: breast metastasis, malignant melanoma, pregnancy

Introduction

The incidence of extramammary neoplasia metastasizing to the breast is low (1.3 – 2.7%) (1), and the great majority of tumors that metastasize to this site is represented by malignant melanoma (MM) (29.8%) (2). Renal adenocarcinoma (3), hematological malignancy, appendicular carcinoid, malignant mesotheliomas, and epidermoid, cervical, pancreatic, rectal (4), ovarian (5), tongue, thyroid and prostate carcinoma (6) have also been demonstrated to metastasize to the breast.

Metastatic melanoma has a very poor prognosis with a 5-year survival rate ranging from 5 to 19%, depending on the position and on the number of metastases (7). Breast metastases from MM could also mimic benign nodules (8,9). Therefore, cytological, pathological and immunohistochemical examinations are necessary to confirm the diagnosis.

Case description

The young patient at issue, a 29-year-old woman, was diagnosed in 2016 with right pre-auricular melanoma (Breslow 1.1mm, IV Clark). She was treated by surgery, followed by enlargement of the operating bed and sentinel lymph node exeresis. In March 2019, she became pregnant. However, a left laterocervical swelling appeared in June 2019, compatible with metastases from melanoma. The patient refused radiotherapy treatment. A mutation in exon 15 of *BRAF* gene was found through genetic analysis of lymph node cytological sample.

In October 2019, seven months pregnant, she presented with palpable mammary left nodule. Therefore, mammographic and elastosonographic investigations were performed, detecting the presence of breast nodule in the left superoexternal quadrant (Figures 1,2).



Figure 1. Left breast ultrasound showing 20 mm mass lesion with well define margin in the upper outer quadrant of the left breast.

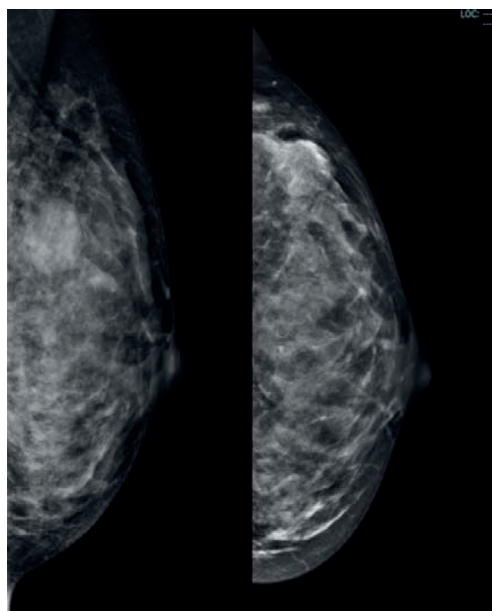


Figure 2. Left mammogram MLO and CC view showing 20 mm lobulated mass lesion in the upper outer quadrant of the left breast.

The clinical and instrumental examination was compatible with benign nodule. In fact, the breast lesion was isolated, roundish, with well-defined margins, in the absence of calcifications and with well-defined posterior wall. To assess a differential diagnosis between corpuscular cyst and fibroadenoma, an aspiration needle was collected, and serum hematic fluid was examined. The cytological results documented the presence of epitheliomorphic cells with atypia of

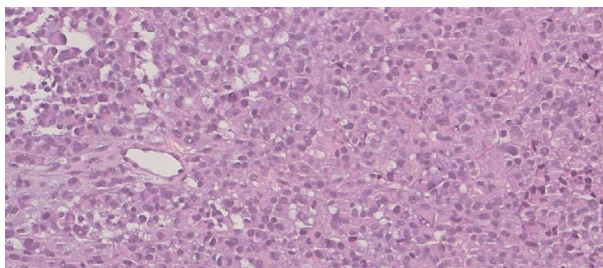


Figure 3. H&E. Metastases of epithelioid melanoma. Neoplastic cells are epitheliomorphic with prominent nucleoli and occasional intranuclear inclusions.

uncertain nature. Subsequently, a needle biopsy was performed. Histological examination revealed the presence of melanoma metastases with immunophenotype CK7- and S100+ (Figure 3).

In December 2019, the patient underwent a cesarean section, that also consisted in the exeresis of the right annex, where metastases from melanoma and extensive necrosis were detected through histopathological examination.

In January 2019, the patient was submitted to contrast enhancement total-body CT scan and to contrast enhancement encephalic MRI which showed the presence of pathological omental nodules, subcutaneous secundarisms, pathologic axillary lymph nodes and encephalic metastases.

Moreover, heterogeneous nodules, indissociable and confluent up to the subcutaneous tissue with retro areolar enhancements were found in the left breast (Figure 4).

Therefore, the patient started Ipilimumab and Nivolumab therapy, and radiotherapy for brain metastases, in addition to antiedema and antiepileptic therapy.

In November 2019, she was reevaluated in our department of breast diagnostics with severe worsening in the mammary context. Multiple palpable nodular formations appeared in the upper external quadrant (the largest of 5 cm) highly suspect of recurrence, that almost entirely replaced the QSE. Several latero-cervical lymphadenopathies were associated, the largest of 2.5 cm.

Unfortunately, patient's exitus occurred in May 2020 due to the progression of the disease.



Figure 4. Contrast enhancement CT scan showing the upper outer quadrant replaced by several solid, uneven nodules, the biggest of 5 cm, which converge among themselves, and extended to subcutaneous tissues.

Discussion

In spite of breast being a rare site of metastases from malignant melanoma, mammographic and ultrasonographic exams should be considered in patients with history of previous melanoma recognizing the aggressive course of the pathology.

Occasionally, breast metastasis can represent the first finding of melanoma of unknown origin (MUP).

A few studies suggest a better prognosis when the primary lesion is unknown(10), while other authors found a similar survival in MUP patients with distant metastases compared to patients with known primary origin at stage IV(11). In about 50% of cases, the site of melanoma breast metastasis is the upper external quadrant, perhaps because of good blood supply and denser glandular tissue in this area (8, 12-14). Breast metastases affect particularly pre-menopausal females (14) probably due to hormonal involvement in melanoma development.

Metastatic nodules can have, radiographically and sonographically, a very aspecific appearance and they can also mimic a benign lesion, such as well-defined hypoechogenic oval nodules with well-defined

posterior wall and no calcifications (8,9). The exclusive characteristic that could discriminate it from benign nodule is usually the vascularity increase of the lesion (15).

However, needle-biopsy and histopathological/immunohistochemical examinations are mandatory to diagnose metastasis of malignant melanoma. No immunochemistry marker is 100% specific or sensitive. In fact, S100 protein is expressed in 95% of melanomas, but it is not specific and should be used with more specific markers, such as Melan A, HMB-45 and tyrosinase. Other markers possibly expressed by these tumors are CD31, CD68, epithelial membrane antigen and CAM 5.2 (16).

In most cases, treatment consists of surgical resection, and chemo, radio or immunotherapy are case dependent.

An interesting aspect of our case is the rapid progression of the mammary neoplastic infiltration by the tumor. The young woman came to our attention in October with a single nodule in the upper external quadrant which appeared radiographically and at the ultrasound examination as a round, circumscribed nodule without infiltration signs, with only one rounded lymph node suspected of metastasis. After a few months, mammographic and ultrasound outcomes completely progressed. Indeed, we found neoplastic infiltration of quite the entire external superior quadrant by highly suspicious nodular formations, the biggest one of about 5 cm, and several axillary lymph nodes, the largest of 2.5 cm. The mammary progression is related to the systemic worsening of cancer, in particular to the presence of ovarian metastases, pathological omental nodules, subcutaneous secondary lesions, pathologic axillary lymph nodes, and encephalic secondarisms. Our case offers a hint about the possible role of pregnancy in the progression of metastatic melanoma.

Even if melanoma is the most common malignancy during pregnancy, the role of pregnancy in tumor development remains unclear. Several theories support the influence of pregnancy in MM, first and foremost that MM could be a hormonally response tumor. There is evidence of Er-Beta receptors in dysplastic nevi with severe atypia and lentigo maligna. Moreover, a strong relation of ER-beta expression

and the proximity of MM cells to keratinocytes was observed (17). Anyhow, the evidence of association of pregnancy with skin hyperpigmentation in selected anatomic areas, the low incidence of MM before puberty, the evidence of estrogen and progesterone receptors in MM and the enhanced growth rate of some MM in mice after administration of estrogen, suggest a key role of hormonal factors in MM (18-21). Several studies have also evaluated the association of oral contraceptive pills (OCPs) and hormonal replacement therapy (HRT) with MM, but as reported in a recent review article, the majority of these studies have shown no effect of oral contraceptive pills compared to who never used them (22).

Another theory suggests that the state of pregnancy immunosuppression may foster the growth and tolerance of cancer cells. Since the maternal-fetal interface diminishes cytotoxic adaptive immune responses in order to protect both mother and fetus from pathogens, immunological tolerance of T helper cell 2 is encouraged. The boost of CD4 and CD25 regulatory cells is essential for fetus survival (23) but these cells also rise in cancer and may be implicated in impaired antitumor immunity, suppression of effector T-lymphocyte proliferation and increased tumor vascularity (24). In particular TH2 transition has been highlighted in a large number of patients with metastatic melanoma compared to patients with resected melanoma (25).

Finally, placenta growth factor, a platelet-derived growth factor, may affect MM growth and spread, though tumor proliferation in response to this factor was only observed in one study (26).

Considering that one third of women diagnosed with melanoma are of child-bearing age (27), fertility preservation should always be evaluated as a crucial factor in melanoma patients' quality life, and fertility counseling should always be provided to all patients of reproductive age who have not completed their family planning.

In particular, given the current limitation of data on potential risk for fertility and subsequent fertility preservation, counseling should be offered to patients who are candidates for adjuvant systemic therapy.

Several options, employed individually or in combinations, are available for women to be considered to preserve fertility: use of gonadotropin-releasing hormone

(GnRH) agonist during gonadotoxic therapy, ovarian stimulation and cryopreservation of unfertilized or fertilized oocytes, and cryopreservation of ovarian tissue.

According to current data, GnRH agonists are discussed (28).

Cryopreservation of ovarian tissue is no longer considered an experimental procedure, and expertise in re-transplantation is growing (29).

Therefore, ovarian stimulation and cryopreservation of unfertilized or fertilized oocytes is currently the first-choice option.

In particular, the use of frozen embryo transfer allows the patient to wait for the ovary to be fully recovered from ovarian stimulation and for the exposed endometrial lining to shed, so better planning makes possible for the patients to have embryos transferred at the ideal time (30).

Moreover, to support the use of frozen embryo transfer, several studies demonstrated a similar risk of perinatal morbidity, mortality and congenital malformations (31) compared to fresh embryo transfer children.

Further studies also focused on psychological aspects of medically assisted reproduction suggesting the key role of preparatory counseling or mind/body interventions (32). Indeed, a futuristic routine approach should involve several healthcare professionals, who collaborate for the physical and mental wellness of patients (33).

In conclusion our case report, in accordance with several cases in literature, suggests a poor prognosis for women diagnosed with metastases of MM during pregnancy, and encourages the mandatory breast examination of women with history of melanoma and the need of fertility counseling in women of child-bearing age diagnosed with metastatic melanoma.

Further studies are needed to assess the correct management of pregnant women with previous diagnosis of melanoma, and to exclude the putative influence of OCPs and HRT in MM development.

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References

- Ravdel L, Robinson WA, Lewis K, et al. Metastatic melanoma in the breast: a report of 27 cases. *J Surg Oncol.* 2006 Aug 1;94(2):101-4.
- Kock A, Ritcher-Marot A, Wissler MP, et al. Mammary metastasis of extramammary cancers: current knowledge and diagnostic difficulties. *Gynecol Obstet Fertil.* 2013 Nov;41: 653-9.
- Saad Abdalla Al-Zawi A, Ratajczak A, Idaewor P, et al. Primary lung cancer with metastasis to the ipsilateral breast—a case report. *Int J Res Med Sci.* 2017;6(1): 334-339.
- Zhou S, Yu B, Cheng Y, et al. Metastases to the breast from non-mammary malignancies: a clinicopathologic study of 28 cases. *Zhonghua Bing Li Xue Za Zhi.* 2014 Apr;43(4): 231-5.
- Recine MA, Deavers MT, Middleton LP, et al. Serous carcinoma of the ovary and peritoneum with metastases to the breast and axillary lymph nodes: a potential pitfall. *Am J Surg Pathol.* 2004 Dec;28(12):1646-51.
- Delair DF, Corben AD, Catalano JO, et al. Non-mammary metastases to the breast and axilla: a study of 85 cases. *Mod Pathol.* 2013 Mar;26(3):343-9.
- Sandru A, Voinea S, Panaitescu E, et al. Survival rates of patients with metastatic malignant melanoma. *J Med Life.* 2014 Oct-Dec;7(4):572-6.
- Moschetta M, Telegrafo M, Lucarelli NM, et al. Metastatic breast disease from cutaneous malignant melanoma. *Int J Surg Case Rep.* 2014;5(1):34-6.
- Jue KF, Lewin JM, Isaacs PK, et al. Unusual sonographic appearance of melanoma metastases in the breast. *J Ultrasound Med.* 2006 May;25(5):663-6.
- Bae JM, Choi YY, Kim DS, et al. Metastatic melanomas of unknown primary show better prognosis than those of known primary: a systematic review and meta-analysis of observational studies. *J Am Acad Dermatol.* 2015 Jan;72(1): 59-70.
- de Waal AC, Aben KK, van Rossum MM, et al. Melanoma of unknown primary origin: a population-based study in the Netherlands. *Eur J Cancer.* 2013 Feb;49(3):676-83.
- Majeski J. Bilateral breast masses as initial presentation of widely metastatic melanoma. *J Surg Oncol.* 1999 Nov;72(3): 175-7.
- Al Samarrae A, Khout H, Barakat T, et al. Breast metastasis from a melanoma. *Ochsner J.* 2012;12(2):149-51.
- Congealet J, Symmans WF, Cohen JM, et al. Malignant melanoma metastatic to the breast: a report of seven cases diagnosed by fine-needle aspiration cytology. *Cancer.* 1998 Jun 25;84(3):160-2.
- Teodorescu EC. Sonography and mammography of primary malignant breast melanoma. *Med Ultr.* 2008 Apr;10(1): 55-8.
- Lee AH. The histological diagnosis of metastases to the breast from extramammary malignancies. *J Clin Pathol.* 2007 Dec;60(12):1333-41.
- Schmidt AN, Nanney LB, Boyd AS, et al. Oestrogen receptor-beta expression in melanocytic lesions. *Exp Dermatol.* 2006 Dec;15(12):971-80.
- Sober AJ, Lew RA, Koh HK, et al. Epidemiology of cutaneous melanoma. An update. *Dermatol Clin.* 1991 Oct;9(4): 617-29.
- Neifeld JP, Lippman ME. Steroid hormone receptors and melanoma. *J Invest Dermatol.* 1980 Jun;74(6):379-81.
- Grill HJ, Benes P, Manz B, et al. Steroid hormone receptor analysis in human melanoma and non-malignant human skin. *Br J Dermatol.* 1982 Nov;107 Suppl 23:64-5.
- Lopez RE, Bhakoo H, Paolini NS, et al. Effect of estrogen on the growth of B-16 melanoma. *Surg Forum.* 1978;29:153-4.
- Gupta A, Driscoll MS. Do hormones influence melanoma? Facts and controversies. *Clin Dermatol.* 2010 May-Jun;28(3): 287-92.
- Leber A, Teles A, Zenclussen AC. Regulatory T cells and their role in pregnancy. *Am J Reprod Immunol.* 2010 Jun;63(6):445-59.
- Holtan SG, Creedon DJ, Haluska P, et al. Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. *Mayo Clin Proc.* 2009 Nov;84(11):985-1000.
- Nevala WK, Vachon CM, Leontovich AA, et al. Melanoma Study Group of the Mayo Clinic Cancer Center. Evidence of systemic Th2-driven chronic inflammation in patients with metastatic melanoma. *Clin Cancer Res.* 2009 Mar 15;15(6):1931-9.
- Lacal PM, Failla CM, Pagani E, et al. Human melanoma cells secrete and respond to placenta growth factor and vascular endothelial growth factor. *J Invest Dermatol.* 2000 Dec;115(6):1000-7.
- Todd SP, Driscoll MS. Prognosis for women diagnosed with melanoma during, before, or after pregnancy: Weighing the evidence. *Int J Womens Dermatol.* 2017 Feb 9;3(1): 26-29.
- Dolmans MM, Taylor HS, Rodriguez-Wallberg KA, et al. Utility of gonadotropin-releasing hormone agonists for fertility preservation in women receiving chemotherapy: pros and cons. *Fertil Steril.* 2020 Oct;114(4):725-738.
- Dolmans MM, von Wolff M, Poirrot C, et al. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. *Fertil Steril.* 2021 May;115(5):1102-1115.
- Gullo G, Scaglione M, Cucinella G, et al. Neonatal Outcomes and Long-Term Follow-Up of Children Born from Frozen Embryo, a Narrative Review of Latest Research Findings. *Medicina (Kaunas).* 2022 Sep 4;58(9):1218.
- Wennerholm UB, Albertsson-Wikland K, Bergh C, et al. Postnatal growth and health in children born after

- cryopreservation as embryos. *Lancet*. 1998 Apr 11;351(9109):1085-90.
32. Kmet LM, Lee RC, Cook LS. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. Edmonton: Alberta Heritage Foundation for Medical Research (AHFMR). AHFMR - HTA Initiative #13. 2004.
33. Burgio S, Polizzi C, Buzzaccarini G, et al. Psychological variables in medically assisted reproduction: a systematic review. *Prz Menopauzalny*. 2022 Mar;21(1):47-63.

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