Pregnancy associated breast cancer: A case report

P.V. Ginopoulos[1], *M.D.*; G.D. Michail[2], G.S. Kourounis[2] *M.D.*

[1]Department of Medical Oncology, "Agios Andreas" Hospital; [2]Obstetrics and Gynecology Department, Patras University (Greece)

Summary

Despite its infrequency, pregnancy associated breast cancer implies multiple therapeutic dilemmas. Our patient, a 32-year-old Caucasian, gravida 2, para 2, was diagnosed with cancer of the left breast in the 19th week of gestation. Shortly after she underwent quadrantectomy plus axillary lymph node dissection. Chemotherapy was initiated in the 22^{+6} week - four cycles of a combination of endoxan, farmorubicin, and fluorouracil. The patient gave birth in the 35^{+6} week to a healthy baby with no apparent malformations. During puerperium she received two more cycles of chemotherapy. She is currently undergoing radiotherapy with tangential fields. Although it is too early to draw conclusions, the malignancy seems to be inactive.

Key words: Breast cancer; Pregnancy; Chemotherapy; Radiotherapy.

Introduction

The coexistence of malignancy and pregnancy is an odd circumstance since these two conditions represent entirely different dynamics. The first is life threatening, while the latter is life reassuring.

The percentiles demonstrated in various articles concerning the ratio of coexistence range widely from 1:1,000 to 1:10,000, whereas more uniform are the data about the dominant types of malignancy, with those of the uterine cervix, malignant melanomas, breast cancer and lymphomas being more common.

Concerning breast cancer, an incidence of 1 in 2,000 pregnancies seems to be a realistic representation. These figures may rise in the future as more women postpone childbearing until later in life. New diagnostic and therapeutic approaches result in making every new case a real challenge for specialists who are involved in the management of patients.

Breast cancer during pregnancy ("PABC" - pregnancy associated breast cancer"), is generally defined as cancer occurring during pregnancy, or within one year of delivery. However difficult the therapy of PABC is, its diagnosis also requires a high index of clinical suspicion due to the radical changes of the mammary gland, while breast engorgement hides solid masses.

Resulting from the often delayed diagnosis, unfortunately the vast majority of patients present with locally advanced disease, or with lymph node involvement, and sometimes with distal metastases at the time of the initial diagnosis. Considering that during pregnancy these neoplasms often appear with negative hormonal receptors and poor immunohistochemical markers, the interpretation of the arising therapeutic issues is a difficult task.

Various tempting hypotheses about the possible interactions between mutations in breast cancer suspectibility genes and breast cancer development during pregnancy, gene "decompression" procedures, etc., try to find the aetiologic sequence, at the same time that the physician faces complex clinical problems, resulting from the fact that he has to decide for two lives, whose interests are not always identical.

Modern trends tend to be in agreement about the surgical procedures allowed during pregnancy (the modified radical mastectomy is still the "gold standard"), while chemotherapy is relatively safe in the second and the third trimester. Tamoxifen should be avoided in the first trimester, and possibly beyond it. The choice of the chemotherapeutic agents is performed under detailed knowledge of their teratogenic potential, in order to eliminate the relative risk. Antimetabolites are the main group of drugs known to generate malformations. It is worth noting that the direct putative toxicity towards the in utero exposed fetus is myelosuppression, which might induce fetal hemorrhage or infection.

Radiotherapy is contraindicated in all trimesters due to the potential for injury to the fetus.

Although termination of pregnancy or therapeutic abortion does not appear to improve survival for the mother, it might be an option if maternal health is jeopardized or fetal anomalies are suspected or confirmed. On the other hand, the obstetrician should weigh the possible advantages of a preterm delivery for a patient in the third trimester with a viable fetus who has to undergo a chemotherapeutic regimen of major toxicity.

Clinical Case

Our patient was a 32-year-old Caucasian, gravida 2, para 2, of middle socioeconomic class, blood group O and Rhesus positive. Family history revealed a rather strong trait for malignancies. The father died of stomach cancer, one of his sisters suffers from breast cancer, and his other sister died of hepatocellular carcinoma.

Revised manuscript accepted for publication September 18, 2003

Referring to the patient's history, there was a beta-thalassemia trait, and concerning the gynecological history, menarche occurred at 12 years of age and the cycle was 28-30 days with heavy menses lasting for eight to nine days. Two months before conception, the patient had a Pap smear (negative for malignancy), but never had a mammography.

Five years before the current conception, the patient gave birth (by cesarean section due to cephalopelvic disproportion) to a healthy female neonate weighing 3,800 g. The mother breastfed the infant for about three to five months.

In the current conception, there was no evidence of threat to the mother's health. Full obstetric care was provided from the initial phases, and the well-being of the fetus was confirmed. Concerning the medication, it consisted of a common regimen in pregnancy (supplements of calcium, folic acid, and ferrum –necessary also due to the beta-thalassemia trait). It was not until the middle of the 16th week of gestation that the pregnant woman realized that an area in her left breast 'was different'. However, as usual with breast malignancies, but maybe more reasonably due to breast changes, there was a delay in seeking expert advice.

In the first clinical examination, shortly before the 19th week, the physician noticed in the upper outer quadrant of the left breast, an area that differed from the proximal hypertrophic mammary gland to an excessive roughness. With that clinical finding, and given that mammography has a high false-negative rate during pregnancy, the doctor suggested that an excisional biopsy (which is the diagnostic procedure of choice for a breast lump during pregnancy) be performed. At this point, we wish to underline the fact that in pregnancy the sensitivity and negative predictive value of FNA (fine needle aspiration) is even lower, leading, even in metastatic disease, women to be falsely reassured.

An excisional biopsy was performed at the end of the 19th week, via a 4.5 cm dissection, and the tissue was frozen sectioned and found positive for malignancy. Shortly after wards on the patient was operated under general anesthesia (quadrantectomy plus axillary lymph node dissection).

Concerning the histopathological report, the frozen section specimen revealed invasive ductal carcinoma, grade 3, with necrosis and lymphangial infiltration in spots. Mitoses were 15/10 HPF, and the neoplasm had a mean diameter of 4.1 cm. In the rest of the tissue of the quadrantectomy, minor neoplastic lesions were found with lymphangial infiltration in spots. In the neighboring mammary gland, there were lesions recognized as in pregnancy, foci of non-typical epithelial hyperplasia of the ducts, and lesions due to fibrocystic disease (cysts, apocrine epithelial hyperplasia). None of the 15 dissected axillary lymph nodes were infiltrated by tumor, even though there were sites of histiocystic reaction. There was no cutaneous involvement.

The performed immunoassays revealed negative estrogen receptors of the tumor and negative progesterone receptors, negative expression of the p53 gene and expression of Ki67. Concerning the expression of C-erb-2/HER-2/neu oncoprotein, the assays were slightly detected in a minor percentile of the cellular population (DAKO Scoring System - Herceptest, score 1/negative) of the main tumor, and for the remaining non-neoplastic tissue the score (under the same scoring system) was 2+/slightly positive. No FISH was performed due to technical reasons.

Due to the impact of the negative anatomical, histopathological, and immunological parameters mentioned above, a sequence of screening tests was performed for staging reasons. The aim was to choose the least intervening exams in order to eliminate fetal distress. A thorough clinical examination was performed, together with ultrasonographic scans of the upper and lower abdomen and the tumor markers. None of these exams presented evidence of metastatic disease. No MRI or PET imaging was performed.

According to the above, the case was evaluated as T_2,pN_0,M_0 and therefore was staged as Stage IIA.

It would be an understatement to claim that the Oncological board (consisting of a clinical oncologist, obstetrician-gynecologist, surgeon, neonatologist, pathologist, radiotherapist, and a psychologist), that reviewed the case shortly after, managed to make the necessary decisions without any emotional impact. However, after taking into account all the parameters, the board decided that the patient would receive adjuvant chemotherapy.

After adequate discussion, the patient signed an informed consent form.

The chemotherapeutic regimen that was selected was 'FEC', consisting of endoxan (dose 600 mg/m^2), Farmorubicin (dose 60 mg/m^2), and Fluorouracil (dose 600 mg/m^2).

Chemotherapy was initiated when the gestational age was 22 weeks and six days, and the planning consisted of six cycles in total, the first four being administered before the scheduled cesarean delivery with intervals of 21 days, and the other two were postponed until after the cesarean delivery. Radiotherapy followed after the sixth cycle.

The reason that led, in the treatment planning, to reserve the 5th and 6th cycle for after the labor, has to do with the recently gained knowledge about the biological actions of the VEGF (vascular endothelial growth factor) in carcinogenesis. It should be noted that the gene expression of VEGF is not only enhanced in the initial phase of carcinogenesis and tumor growth, but also after every surgical manipulation. This accelerates the formation of vessels (for blood supplementation to the tumor) and perhaps the metastatic procedure. At this point let us recall Hippocrate's words 'Don't touch the bad blemish' (...). By reserving the last two cycles until after the scheduled cesarean section, we would both destroy the micrometastases, which until then had been suppressed by the gestational hypercortisolemia, and prevent any putative 'flare up' of new foci with the VEGF increase.

Chemotherapy was suspended with granulocyte stimulating factor administration (for 7-8 days, s.c., after each cycle), recombinant human erythropoeitin (r-HuEPO, 40,000 I.U., twice weekly after each cycle, not necessary only due to the malignancy, gestation, chemotherapeutic toxicity and the following cesarean delivery, but also due to the beta thalassemia trait), and the common antiemesis and H2 antagonists. The patient tolerated full doses of the chemotherapeutics without major complications given that she presented only mild GI symptoms (nausea and vomiting, grade 1).

Great attention should be given to the fact that one of the commonest toxicities of the regimen is alopecia (usually grade 4), which was not a presenting sign of our patient. Considering that this is extremely rare, it should still be addressed given certain hormonal particularities of a gestation.

The pregnancy continued and high-risk obstetric care was provided. Emphasis was placed on intensive fetal surveillance. Serial fetal growth ultrasound examinations were performed every three to four weeks. Fetal nonstress testing was performed beginning at the 28th week. After the 30th week, the mother developed gestational diabetes and was managed well by dietary modifications. To which extent this complication was due to chemotherapy is uncertain, although it was not present in the previous gestation.

Labor was planned via cesarean section because of a previous cesarean section, and corticosteroids were administered to

lessen the neonatal sequelae of putative prematurity. At the gestational age of 35 weeks and two days, the patient was admitted to the Obstetrics Clinic due to premature rupture of the fetal membranes. Various obstetrical indications (mainly the appearance of uterine contractility, given the previous cesarean section), led to the decision to accelerate the new cesarean section just four days later.

Concerning perinatal outcome, the Apgar score was 8, and the female infant weighed 3,420 g., a very satisfactory weight for that gestational age, perhaps due to the mother's diabetes. No congenital malformations were noted. The infant presented a mild episode of transient tachypnea, requiring oxygen support. All blood exams performed in the Neonatal Unit were within the normal range, and shortly after, the infant was given to the parents. The psychophysical development of the newborn will be followed-up.

The first days of the puerperium were uncomplicated, with a subclinical leucocytosis, and the 5th postoperative day - one day later than usual - the patient was discharged from the clinic.

It is obvious that breast feeding was prohibited as a consequence of chemotherapy exposure.

After a 20-day period, the patient recommenced chemotherapy as planned. The remaining two cycles were administered with a 21-day interval, with similar parameters as the preoperative ones, and without severe toxicity.

Twenty days after finishing chemotherapy the patient initiated the planned radiotherapy. The intention was to administer radiotherapy to the entire tumor bed, with tangential fields, at a total dose of 4500-5000 cGy during a 4.5-5 week period that the patient would undergo at that time.

Despite being too early to draw any conclusions, nothing indicates at the time that the malignancy is active. The patient complains of an annoying 'feeling of tension' at the surgical scar, but this does not correspond clinically with recurrence.

Only continued follow-up will demonstrate the mother's recovery and absence of consequences to the newborn from the chemotherapeutic agents.

Discussion

Although most of the following were cited before, we would like to underline:

I) In very few cases today is the decision to terminate a pregnancy justified, especially in the 2nd or 3rd trimester.

II) The management of these cases is best served by the early and continuing involvement of a multidisciplinary cancer treatment team.

III) The current trends in oncology, permit the administration of efficient chemotherapeutic regimens which do not seem to seriously affect the fetus.

IV) A great era for research due to the changes in pharmacokinetics and pharmacodynamics of the chemotherapeutic agents, which are probably attributable to the normal compensating mechanisms of gestation.

V) Is the process of breast carcinogenesis in pregnancy identical to the one in non-pregnant women? Is it induced from the complex hormonal profile or are some particular genes activated, or both?

Despite these points, the physician must keep in mind that modifications made in his therapeutic alternatives, while treating breast cancer in order to achieve the birth of a healthy child, may adversely suppress the mother's chances for permanent therapy.

However, it is almost certain that soon the advances in therapeutics and continuing medical care, will ameliorate even more the parameters of the mother's and neonate's morbidity.

References

[1] Helewa M., Levesque P., Provencher D., Lea RH., Rosolowich V., Shapi H.M.: "Breast cancer, pregnancy, and breastfeeding". *J. Obstet. Gynaecol. Can.*, 2002, *24* (2), 164.

[2] Mignot L.: "Cancer of the breast and pregnancy: the point of view of the breast cancer specialist". *Bull. Cancer,* 2002, *89* (9), 772.

[3] Pautier P., Lhomme C., Morice P.: "Cancer and pregnancy: the point of view of the chemotherapy oncologist". *Bull. Cancer,* 2002, *89* (9), 779.

[4] Mathieu E., Merviel P., Antoine J.M., Uzan S.: "Cancer and Pregnancy: the point of view of the obstetrician". *Bull. Cancer,* 2002, *89* (9), 758.

[5] Weisz B., Schiff E., Lishner M.: "Cancer in pregnancy: maternal and fetal implications". *Hum. Reprod. Update,* 2001, *7* (4), 384.

[6] Keleher A.J., Theriault R.L., Gwyn K.M., Hunt K.K., Stelling C.B., Singletary S.E. *et al.*: "Multidisciplinary management of breast cancer concurrent with pregnancy". *J. Am. Coll. Surg.*, 2002, *194* (1), 54.

[7] De Santis M., Lucchese A., De Carolis S., Ferrazani S., Caruso A.: "Metastatic breast cancer in pregnancy: first case of chemotherapy with docetaxel". *Eur. J. Cancer Care,* 2000, *9* (4), 235.

[8] Healy C., Dijkstra B., Kelly L., McDermott E.W., Hill A.D., O' Higgins N.: "Pregnancy-associated breast cancer". *Ir. Med. J.,* 2002, *95* (2), 51.

[9] Gwyn K.M., Theriault R.L.: "Breast cancer during pregnancy". *Curr. Treat. Options Oncol.,* 2000, *1* (3), 239.

[10] Rugo H.S.: "Management of breast cancer diagnosed during pregnancy". *Curr. Treat. Options Oncol.*, 2003, *4* (2), 165.

[11] Pavlidis N.A.: "Coexistence of pregnancy and malignancy". *Oncologist,* 2002, *7* (4), 279.

[12] Crivellari D., Lombardi D., Scuderi C., Spazzapan S., Magri M.D., Gioro G. *et al.*: "Breast cancer and pregnancy". *Tumori,* 2002, *88* (3), 187.

[13] Berry D., Theriault R.L., Holmes F., Parisi V., Booser D.J., Singletary E. *et al.:* "Management of breast cancer during pregnancy using a standardized protocol". *J. Clin. Oncol.,* 1999, *17* (3), 855.

[14] Woo J.C., Yu T., Hurd T.C.: "Breast cancer in pregnancy: a literature review". *Arch. Surg.,* 2003, *138* (1), 91.

[15] Giannakopoulou C., Manoura A., Hatzidaki E., Froudarakis G., Koumandakis E.: "Multimodal cancer chemotherapy during the first and second trimester of pregnancy: a case report". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2000, 91.

[16] Cammisuli F., Catania V., Santuccio A., Mirone I., Pagano P., Cavallaro A.: "Breast carcinoma in pregnancy: a clinical case". *Ann. Ital. Chir.,* 2002, *73* (3), 317.

Address reprint requests to:
G.S. KOUROUNIS, M.D.
Associate Professor of Obstetrics
and Gynaecology
Patras University
2 Terpsitheas str.,
26442 Patras (Greece)