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Presentation, management and outcome of 13 patients with pregnancy-associated breast cancer: a case series

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Abstract: Background: *Cancer is the 2nd cause of death among women aged 25 to 44 (2), which makes the association of cancer and pregnancy possible purely by chance. Breast cancer associated with pregnancy (PABC) is a complication found around 1 in 10 000 to 1 per 3,000 pregnancies. It is one of the most common cancers associated with pregnancy (3) this case series aims to study the presentation management and prognosis of pregnancy-related breast cancer.* ***Patients and methods:*** *Data concerning patients' and tumors' characteristics, management, delivery and maternal outcome were recorded from institutional electronic database. In this case series we collected data from PABC patients treated at the UTH Hassan II fez Morocco, between January 2016 to April 2022. The key recommendations on managing such patients are summarized.* ***Results:*** *The histological type was found on invasive ductal carcinoma, in 92,3% cases. The ACR classification was performed in 13 patients: ACR 0 in 1 patient (8%), ACR 4 in 4 patients (31%) and ACR 5 in 8 patients (61).Therapeutically, 69.23% of the patients were treated with the Patey procedure. Chemotherapy was administered in 11 patients. 8 patients received neoadjuvant chemotherapy 72.72%, including 4 patients who were pregnant, only 2 patients. Received adjuvant chemotherapy 18.18%, and only 1 patient received palliative chemotherapy 9.09* ***Conclusions:*** *Women with pregnancy associated breast cancer should be managed like non-pregnant breast cancer patients and should expect a similar outcome, without causing harm to the unborn child. To achieve a good outcome in pregnancy associated breast cancer, a multidisciplinary approach is mandatory. Pregnancy-related breast cancer tends to be diagnosed in an advanced stage with poor prognosis. Any breast abnormalities observed in this period should alert clinicians, and a meticulous radiological evaluation is mandatory. The early diagnosis of this disease would increase the chances of successful treatment.*

Keywords: Pregnancy associated breast cancer (PABC), Gestational, Trimester, Antepartum, Post-partum

1. INTRODUCTION

Breast cancer is the most common cancer among women worldwide. It represents 32.2% of all female cancers and it is estimated that a woman has a 10% probability of being affected until the age of 74 (1). According to the World Health Organization (WHO), more than a million new cases of breast cancer are diagnosed worldwide and more than 400,000 women die every year.

Cancer is the 2nd cause of death among women aged 25 to 44 (2), which makes the association of cancer and pregnancy possible purely by chance. Pregnancy associated breast cancer (PABC) is a complication found in between 1 in 10 000 to 1 per 3,000 pregnancies. It is one of the most common cancers associated with pregnancy (3) this case series aims to study the presentation management and prognosis of pregnancy-related breast cancer.

Pregnancy-associated breast cancer or PABC is defined by the occurrence of breast cancer during pregnancy or during the year following childbirth (4). The incidence of pregnancy-associated breast cancer is increasing due to the increase in the age of pregnant women and the overall increase in the incidence of breast cancer. This association represents 10% of breast cancers in women under 40 years old (5).

To this classic definition, most teams also associate the cancers that are seen after an abortion or terminated pregnancy. It's the first pregnancy-associated cancer (6). The concomitant occurrence of these two clinical entities poses different diagnostic, then therapeutic and finally prognostic problems (7):

- Diagnosis: due to changes in the mammary gland that make the difficult diagnosis, and mammogram which loses its sensitivity when faced with breasts dense hypertrophied. (8)

- **Management**: where conduct must take into account contraindications to chemotherapy, radiotherapy and the consequences on the evolution of the pregnancy.

- **Prognosis**: pregnancy is known to have a pejorative influence on the evolution of cancer, particularly due to the frequency of advanced forms inflammatory diseases affecting the maternal and fetal prognosis.

2. METHODS

Our study concerns a series of 13 patients who presented the association of breast cancer during their pregnancy. We included patients in whom the breast cancer was discovered during an active pregnancy or within 12 months post-partum. We excluded patients in whom the diagnosis of breast cancer was placed after an abortion or a terminated pregnancy.

Firstly, the data was collected from the files medical conditions of patients at the Gynecology Obstetrics department, supplemented by data from the statistics office and the emergency department gyneco-obstetrics of the CHU-HASSANII of Fez.

Secondly, telephone interviews were carried out to determine the evolution of these patients and to assess the well-being of the children born of these pregnancies.

2.1. Statistical analysis

Descriptive statistics were used for reporting the patient, tumor and treatment related characteristics. The data was entered using Excel 2010 software and analyzed using the software. IBM SPSS 23.0.

Quantitative variables were described as averages, while qualitative variables were described in terms of proportions. The study protocol was submitted to the Hospital Ethics Committee. University of Fez and received his approval.

3. RESULTS

3.1. Study population

The average age of our patients is 35.07 years with extremes ranging from 22 to 42 years. The average age of menarche was 14 years. The average parity was 3 children per woman and it was found that the majority of patients breastfed their children, i.e. a percentage of 71%. Eight of our patients had already taken estrogen-progestin contraception, i.e. 61, 53% variable duration. A single patient had a history of breast cancer. No toxic habits were reported by the patients in our series. Only one patient had a sister who died of breast cancer. The average consultation time was 7.3 months. Palpation of an isolated breast nodule was the first reason leading to a consultation in 9 of our patients, i.e. 69.23%.

Breast cancer was diagnosed during pregnancy in all patients. The average term at the time of diagnosis is 20.53 weeks. We therefore see that 53.84% of tumors are diagnosed at a locally advanced stage (T3 or T4). Breast inflammation was noted in one patient, i.e. a percentage of 7.69%. Axillary lymphadenopathy was palpable in 7 patients.

3.2. Radiological findings

Mammography was performed in 12 of our patients (with cover). It was suspected of malignancy in 9 patients or 75% showing malignancy criteria

Ultrasound was done in all our patients, with suspicious findings in 12 patients or 92.3%, showing major criteria of malignancy: heterogeneous hypoechoic lesion (12 patients), the contours were spiculated (5 cases), micro lobulated (4 cases), polylobed (3 cases). In only one patient the ultrasound came back normal.

Two of our patients had breast MRI.

The thoraco-abdominopelvic scan was performed in 8 patients as an extension assessment.

3.3 pathological findings.

The biopsy was performed in all our patients:

The histological type was specified in all patients who received a breast biopsy:

- An infiltrating ductal carcinoma of the NOS type in 12 patients or 92.3%.A poorly differentiated adenocarcinoma of breast origin (biopsy of an ADP axillary) in a single patient.

Histoprognostic grading of Scarff Bloom and Richardson (SBR) was quite high with grade II in 58% of cases, and grade 3 in 42% of cases.

. Hormonal receptors and HERCEPT test was carried out on all our patients. They are positive in 7 patients, or 54% of cases, and negative in 6 patients, or 46% of cases.

Molecular classification was carried out in all our patients:

- Luminal A in 3 patients or 23.07%, Luminal B in 1 patient or 7.69%, Her 2 positive in 6 patients or 46.15%, Triple negative in 3 patients or 23.07%.

3.4. Oncological treatments

3.4.1 Management of breast cancer

a.Surgery :

Mastectomy for curative purposes was performed in 9 patients, or 69.23% of cases. Axillary lymph node dissection was performed in 9 subjects, or 69.23% of cases. Postoperative complications were found in one of our patients who had a post-operative lymphocele and one of our patients had lymphedema

b. Chemotherapy:

11 patients received chemotherapy, i.e. 92.30% of cases.8 patients benefited from neoadjuvant chemotherapy, i.e. 72.72%, of which 4 patients were pregnant, 2 patients in the 2nd trimester and the other 2 in the 3rd trimester of pregnancy, note that no patient presented complications maternal or fetal specifically linked to pregnancy following neoadjuvant CMT.Only 2 patients benefited from adjuvant chemotherapy, i.e. 18.18%.Only 1 patient benefited from palliative chemotherapy, i.e. 9.09%

c. Radiotherapy:

Radiotherapy was carried out in 8 of our patients, or 61.53% of cases.

d. Hormonal therapy:

6 of our patients received hormonal therapy, i.e. 46.15% of cases. Adjuvant hormonal therapy: 5 patients received tamoxifen, i.e. 38.46%.1 patient had received palliative hormonal therapy, i.e. 7.69% of cases. 6 patients benefited from treatment with Trastuzumab 38.46%.

3.5. Survival analysis

a. Evolution and Morbi-mortality:

The average follow-up is 43.81 months with extremes of 14 and 82 months in 11 patients who are still alive including 2 metastatic patients. One patient presented with liver metastasis. 2 patients were lost to follow-up and 0 deaths among the 11 patients monitored.

3.5.1 Pregnancy related details

1. Obstetric care:

3 of our patients benefited from a Therapeutic Termination of Pregnancy with medication after pluri disciplinary consultation and the ethics committee.

A Growth curve every 3 weeks with Doppler monitoring of the umbilical artery. Monitoring every 15 days of the Doppler of the umbilical and cerebral artery, the quantity of amniotic fluid, the presence of the bladder as well as growth in the patient with a twin pregnancy.

2 patients gave birth at term, i.e. 20%. Premature delivery was found in the 8 other cases, i.e. 80%: Induced prematurity in 6 patients after a course of corticosteroid therapy, Spontaneous delivery before 37 weeks in the 2 other patients.5 women had given birth vaginally, i.e. 50% of the patients, including 2 spontaneous births and 3 births after induction in patients who had received a course of corticosteroid therapy.

C section: 5 women had given birth vaginally, i.e. 50% of patients. The birth weight of newborns averaged 2,674.76 g and varied between 2000g and 3500g. The neonatal prognosis was assessed by the Apgar score at 5 minutes of life which was in average of 9.78/10. The psychomotor development of 4 newborns was normal. The other patients could not be reached. A copper intrauterine device was prescribed in 11 patients or 84.62%. While the use of condom was prescribed in 2 patients or 15.38%

4. DISCUSSION

Pregnancy-associated breast cancers (pregnancy-associated breast cancers) complicate between 1 in 10,000 and 1 in 3,000 pregnancies. It is one of the cancers most frequently associated with pregnancy: the first cancer associated with pregnancy in the American study by Van Calsteren et al. (9) involving 215 patients with cancer during pregnancy with 46% of cancers associated with pregnancy in this population; third cancer associated with pregnancy (10%) after melanomas (27.3%) and cervical cancers (18.2%) in the Norwegian study by Sternheim et al. In our series, the frequency is 0.73% of breast cancers, which is similar to the figures in the literature. (14) Several studies estimate the average age of affected women to be 31 to 36 years (14). This tends to increase, due to increasingly late pregnancies, particularly in the event of recourse to medically assisted procreation (AMP). In our series, the estimated average age is 35.07

The diagnosis is often made later than outside of pregnancy, which partly explains the more advanced and progressive forms of PABC. Indeed, a delay of 1 month increases the risk of axillary lymph node metastases by 0.9% for a tumor splitting time of 130 days, 6 months of delay increases the risk by 5.1% (10).

The method of revealation PABC is usually self-palpation by the patient of a generally tender breast mass. More rarely, it involves the discovery of bloody nipple discharge during pregnancy and breastfeeding, nipple retraction, an inflamed breast or the discovery of axillary lymphadenopathy.(11) (12)(13)(16) A clinical case of rejection of the cancer-bearing breast by the newborn out of disgust has been reported (17). The use of mammography as a means of investigation is debated because it is criticized on the one hand for irradiating the child and on the other hand for its low diagnostic yield during pregnancy (18).

Difficulties in diagnosis are linked to physiological changes which lead to a diffuse and marked increase in breast density. On mammography, the glandular tissue appears very dense, heterogeneous in distribution, sparse or nodular and confluent in appearance. The fatty contingent decreases and the milk structures are hypertrophied. These elements, associated with high glandular density in young women, significantly reduce the sensitivity of mammography, usually established between 70 and 90%. However, these signs are not constant and the glandular density may be unchanged. If the woman is breastfeeding, it is recommended to perform the mammogram immediately after breastfeeding. Mammography was performed in 12 of our patients (with cover). It was suspected of malignancy in 9 patients or 75% showing criteria for malignancy. This is the first-line clinical examination in this case and must be performed in front of any palpable mass (20). Breast ultrasound has the best sensitivity (close to 100%) for the diagnosis of breast cancer associated with pregnancy, especially since the increase in breast density linked to pregnancy in these young patients reduces the performance of the mammography. Bilateral breast ultrasound is therefore recommended as first intention in all pregnant patients without harmful effects for the fetus (21) (22) (23) (24). Approximately 90% of women with CSAG have a mass easily detected on ultrasound (25) (26). Breast MRI has no place in the diagnosis of a breast anomaly in pregnant or breastfeeding women (23).

The cytological puncture remains an essential diagnostic tool, it will make it possible to differentiate a cyst, a galactocele from a solid mass. It is an easy examination, and accessible during pregnancy, although it is considered technically more difficult to perform due to breast engorgement (27). microbiopsy and excisional biopsy seem more suitable for making the diagnosis with certainty, given the difficulty of cytological interpretation.

There is no specificity of the histological types and the immunohistochemical characteristics of CSAG, the histological types are identical to those of young non-pregnant women. Mostly, the different histological types of BC occur at the same frequency in pregnant women. (29)

Hormonal receptors are essentially predictive but also prognostic factors. They are called predictive because if the patient is receptor positive, she can benefit from hormonal treatment. At the same time, they are called prognostic because their presence is associated with a better prognosis. It showed that there was a significantly higher and earlier frequency of recurrences for patients who were estrogen receptor negative than for those who were receptor positive. (30)

The treatment of breast cancer involves surgery, radiotherapy, chemotherapy and hormonal therapy, variously combined. These treatments must take into account two imperatives: the treatment of cancer in a young woman, who is pregnant, without harmful delay; respect for the embryo and the fetus at its various stages of maturation, as far as this is compatible with the need to properly treat maternal pathology (28). The management of a CSAG in a postpartum patient does not pose a specific problem and is identical to that of a patient with breast cancer not associated with pregnancy with the same tumor characteristics. It is ideally as close as possible to that which the patient would benefit from if she were not pregnant (15). Nevertheless, pregnancy requires "adjustments" in therapeutic protocols, the aim being to reconcile continuation of pregnancy and anti-tumor treatment, by minimizing fetal risks on the one hand and avoiding delayed or suboptimal oncological treatment of elsewhere (31). The effect of chemotherapy on the fetus appears to depend on the type, duration and doses of cytotoxic drugs used, as well as gestational age

During the first four post-conception weeks, cellular differentiation and organogenesis are minimal. The cytotoxicity of chemotherapy will therefore lead to either the spontaneous termination of the pregnancy or no effect (all or nothing law). During the weeks following the first trimester, chemotherapy can interfere with organogenesis with a significant teratogenic risk (32) (33), this is the most vulnerable phase of gestation (15). It can be used beyond 14 weeks with few side effects (fetal hypotrophy, prematurity, in utero fetal death and rare cases of neonatal cytopenia reported) (34).

The most documented treatments are doxorubicin, cyclophosphamide and 5-fluorouracil in the treatment of breast cancer.

For a long time, termination of pregnancy was considered to improve the prognosis of breast cancer, and was systematically proposed (19). Obstetric care has not been the subject of any specific recommendations. At the time of diagnosis, it is necessary to ensure the absence of fetal anomalies pre-existing treatments by obstetric ultrasound. Postpartum, oncological treatments can be resumed immediately after an uncomplicated vaginal delivery and after a delay of one week in the case of an uncomplicated cesarean section. After chemotherapy, breastfeeding is not recommended due to the accumulation in milk of fat-

soluble chemotherapies such as taxanes. When a CS is discovered during the breastfeeding period, stopping breastfeeding is recommended

CONCLUSIONS:

Women with pregnancy associated breast cancer should be managed like non-pregnant breast cancer patients and should expect a similar outcome, without causing harm to the unborn child. To achieve a good outcome in pregnancy associated breast cancer, a multidisciplinary approach is mandatory. Pregnancy-related breast cancer tends to be diagnosed in an advanced stage with poor prognosis. Any breast abnormalities observed in this period should alert clinicians, and a meticulous radiological evaluation is mandatory. The early diagnosis of this disease would increase the chances of successful treatment.

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