Ovarian Cancer After Breast Cancer Treatment: Study of 03 Cases in a Guinean Oncological Setting

Bah Malick*, Toure Alhassane Ismael, Keita Mamady, Cisse Kalil, Souare Mamadou Bozo, Conde Ibrahima Kalil, Cisse Mohamed Falliou, Traore Bangaly

Surgical Oncology Unit at Donka National Hospital, Conakry University Hospital, Conakry, Guinea

Email address:
lickmadem@yahoo.fr (Bah Malick), tourealhassane@yahoo.fr (Toure Alhassane Ismael), mamadykeita@rocketmail.com (Keita Mamady), mbohosouare@gmail.com (Souare Mamadou Bozo), condekali1800@gmail.com (Conde Ibrahima Kalil),
ucodonk@ac.com (Traore Bangaly)

*Corresponding author

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Abstract: Introduction: Ovarian cancer, the 1st cause of death from gynecological cancer, is any malignant proliferative process developed in the ovary, which may occur after a treated breast cancer. Objectives: To discuss the management and prognosis of ovarian cancer after breast cancer treatment through a series of 3 clinical cases in a Guinean oncology setting. Case 1: A 60-year-old patient presented with an ulcerating tumor of the uterine cervix, after treatment of a CCI, she benefited from 12 courses of palliative chemotherapy and died 04 months after her last course with decompensated anemia. Case 2: the 75-year-old female patient who presented with abdominal distension with ascites associated with a pelvic mass after treatment of a CCI, died of multivisceral failure. Case 3: A 61-year-old hypertensive diabetic patient presented with abdominal distension and a pelvic-abdominal mass. After treatment of a CCI, she underwent an exploratory laparotomy and died at D15 post-op in hypovolaemic shock. Conclusion: This study shows the need to include monitoring of gynecological organs in patients treated for breast cancer. The diagnosis was late and the prognosis was poor.

Keywords: Ovarian Cancer, Treatment, Breast Cancer, Guinean Oncological Environment

1. Introduction

Breast cancer is the most common cancer and remains the leading cause of cancer-related death in women [1].

Ovarian cancer is the 5th most common cancer after breast, colon, cervical, and corpus uteri, and is the 3rd leading cause of cancer death [2].

Although the management of ovarian cancer is well established, less is known about the patterns of ovarian cancer in breast cancer survivors [3].

The discovery of an ovarian mass in a woman with a history of breast cancer raises the question of its primary or secondary origin [4].

However, after breast cancer, there is a slight increase in the risk of second primary cancer (SIR between 1.15 and 1.46). Women diagnosed with breast cancer before the age of 40 have a 3-fold increased risk of PCS [5]. Usually, the most frequent metastatic sites for breast cancer are the lung, bone, and liver, with ovarian metastasis appearing as a less well-known but not exceptional possibility after treated breast cancer [6].

The frequency reported in the literature of ovarian metastases from breast cancer is around 20 to 30%, varying according to the study (autopsy, therapeutic castration, or clinical) [4].


In Tunisia, Zoukar et al [4] reported 3 cases of genital breast cancer metastases, 2 of which were ovarian.

The discovery of an ovarian mass in a woman with breast cancer represents a primary ovarian tumor 3 times or more
often than a metastasis [4].

However, the clinical difficulty in distinguishing between the ovarian metastatic progression of breast cancer and the occurrence of a second primary ovarian cancer in a patient previously treated for breast cancer, and the need for information on their management, prompted the present study, the aim of which was to:

Discuss the management and prognosis of ovarian cancer after breast cancer treatment through a series of 3 clinical cases in a Guinean oncological setting.

2. Presentation of Cases

2.1. Clinical Case N° 1

A 60-year-old patient with a surgical history of extra uterine pregnancy (EP) in 1999 and mastectomy with axillary curage (MCA) in 2014; family history of 1st-degree breast cancer (her sister). We have no information on the patient's BRCA molecular profile. She had her first menstrual period at the age of 14, her first pregnancy at the age of 22, and has undergone eight gestures, seven parities, and one abortion. Menopausal for 10 years. She had been on oral contraception for 3 years. She was not on hormone replacement therapy (HRT).

She consulted the surgical oncology unit (UCO) for pelvic pain, metrorrhagia, and hydrorrhoea. The onset of the disease was four years ago, marked by the appearance of a nodule in the left breast, detected by auto palpation. She consulted the UCO for treatment, where a cytopsy of the left breast was performed, suspicious. The result of the anatomopathological examination of the biopsy specimen was suggestive of infiltrating ductal carcinoma (IDC) grade SBRII. The frontal chest X-ray showed sequelae of left pachypleuritis and the abdominopelvic ultrasound was unremarkable.

She was diagnosed with an infiltrating ductal carcinoma of the left breast classified as pT2N0M0 stage IIA, for which she was to receive neoadjuvant chemotherapy under the EC100 protocol (Epirubicin 100mg - Cyclophosphamide). Lost to follow-up, the patient presented 10 months later at the MEDISAR polyclinic for post-treatment monitoring after a stay in Morocco where she had undergone radical mastectomy followed by 06 courses of adjuvant chemotherapy under the protocol (3FEC100+3Docetaxel), 42Gy radiotherapy in 15 sessions on the chest wall and underwent hormone therapy of the Letrozole type at the Hassan II FES University Hospital for RH+ breast cancer; HER2-; luminal B; classified pT2N1M0 stage IIB. Clinical evaluation revealed lymphoedema of the homolateral upper limb with no sign of locoregional recurrence. Quarterly surveillance was the norm. Nine months later, the patient was seen with phlegmon on a large arm associated with intense pain; we proceeded to flatten the phlegmon with a drain, antibiotic therapy, and analgesics. During her surveillance, the patient developed an acute psychotic state with delusions and was put on specific treatment after psychiatric consultation. Over the following months, the psychotic symptoms resolved. However, she returned to the UCO for consultation with pelvic pain associated with metrorrhagia and hydorrhoea.

The patient was hypocoloured on the WHO Performance Index = 02. The abdomen was symmetrical, with a median sub-umbilical scar, soft, painless, and without any palpable mass; on vaginal touch (VT): the vaginal wall was soft. On speculum examination, an ulcerated and burgundy cervix was noted, bleeding on contact and invading the upper 1/3 of the vagina; on rectal examination (RE), the fingernail felt a submucosal tumor infiltration of the fixed rectal wall located 6 cm from the anal margin between 4 and 12 o’clock, with infiltration of the left parametrium. The lymph nodes were free; elsewhere, a hard MCA scar was noted, with no sign of loco-regional recurrence.

Given the tumor at cervical level bleeding on contact, we thought of a malignant tumor of the uterine cervix classified as FIGO stage IVA following breast cancer treated with IOMS=02.

A colonoscopy revealed atony of the recto-sigmoid junction and a protruding deformity of the rectal mucosa, possibly related to extrinsic compression.

The biological work-up did not show any particularities.

We planned a transrectal biopsy, which was not carried out due to the patient's absence.

The patient presented 10 months after returning from Morocco, where a pelvic MRI revealed: Two (02) bilateral lateral-uterine masses, mostly solid-cystic with necrosis of 7.6*5.6cm invading the cervix, vagina and upper rectum with a fistula on the right and mostly cystic with parietal vegetation of 6, 9*5.5*6.5cm invading the sigmoid as well as the uterine body and endometrium on the left associated with a nodule of carcinosis measuring 17mm for the largest and a left external iliac adenopathy measuring 14mm (Figure 1).

Figure 1. Transverse axial section showing a left ovarian mass and rectal thickening on MRI.
Pathological examination of the cervical biopsy specimen confirmed a poorly differentiated endometrioid adenocarcinoma. On immunohistochemistry (P16; CK7 and RE); CK7 intensely expressed; CK5/6−; no GATA3 expression; RE+; intense expression of P16 protein.

The diagnosis of a poorly differentiated endometrioid ovarian adenocarcinoma was made in a 60-year-old female patient with a history of acute rheumatic fever, EP, MCA, and first-degree cancer; the disease occurred after radical treatment of left breast cancer treated with surgery, adjuvant chemotherapy, radiotherapy and hormone therapy on IOMS=02.

The patient underwent initial chemotherapy using the carboplatin-paclitaxel protocol in Morocco. She received 06 courses with partial regression of the pelvic mass and the left lymph node mass.

The follow-up TAP scan showed almost complete disappearance of the pelvic mass in the right lateral-rectal region, with the persistence of a residual mass currently measuring 43*22*mm vs 63*51mm, and regression in size of the left iliac lymph node mass coming into contact with the uterus, currently measuring 48*37mm vs 61*45mm (Figure 2).

At a gynecological consultation meeting (RCP) in Morocco, after reviewing the radiology, surgery was not feasible. It was therefore decided to add 02 other treatments and then carry out surveillance. The patient, therefore, underwent 08 courses of chemotherapy in Morocco. The patient returned to us 8 months after her last course of chemotherapy in Morocco. Following a PCR, we decided to add 04 courses of chemotherapy using the same protocol. Four months after her last course of chemotherapy, the patient presented with anemia of 6.4 g/dl and thrombocytopenia of 36 G/L (grade IV); she had received one bag of 0+ packed red blood cells and 2 bags of fresh plasma. She died 24 hours after an emergency admission to the MEDISAR polyclinic with decompensated anemia.

2.2. Clinical Case 2

This was a 75-year-old patient with no known medical history and a history of MCA surgery in 2012. No family history of cancer was reported, however, the patient's BRCA molecular profile was unknown. She had her first pregnancy at the age of 20, has had 8 pregnancies, 8 deliveries, and is menopausal. However, her menarche, the date of her last menstrual period, and the cycle and duration of her periods are not known. She has never been on oral contraception or hormone replacement therapy (HRT).

The disease began eight (8) years ago, when a poorly defined retroareolar nodule on the left breast retracted the nipple, prompting a consultation during which a mammogram showed a malignant nodule. Given the result, she was evacuated to Switzerland where, after investigation, she underwent MCA with a simple postoperative course, followed by 4 courses of adjuvant chemotherapy under the Hydroxy adriamycin-Endoxan (AC100) protocol; followed by 4 courses of Taxol monotherapy with clinical tolerance marked by asthenia and grade III alopecia. Post-operative radiotherapy with a total dose of 50Gy delivered to the chest wall, followed by a 10Gy boost to the supra- and infra-clavicular lymph nodes, for a total dose of 60Gy. Clinical tolerance was marked by radiodermatitis. The onset of a dry, persistent cough after 36 months prompted a further consultation in the pneumo-phthisiology department of the Ignace-Deen Hospital, where a frontal chest X-ray was ordered, demonstrating an accentuation of the bronchovascular framework in the hilar region. She was then referred to the UCO for post-therapy monitoring of a CCI of the left breast classified as pT2N1M0R0, triple negative (EP-, PR-, HER-). Post-therapy monitoring was carried out quarterly. Over 04 months we did not observe any particularities. After 04 months, she presented with a cough associated with mucopurulent sputum and presented with crepitating rales more accentuated in the right lung field and sibilant rales in the left lung field; there was no sign of loco-regional recurrence. A chest X-ray showed cardiomegaly; there were no signs of pleurapulmonary metastases. We requested a cardiology consultation, which revealed a systolic ejection fraction of 28%, and a hypokinetic dilated left ventricle with predominant septal defects, and the patient was put on Aspegic 100mg and Digoxin 0.25mg. Cardiological monitoring was the rule. The patient presented five years after her first consultation at the UCO with abdominal distension.
associated with a dry cough.

The patient had a WHO Performance Index of 02. The abdomen was distended with a positive float sign; deep palpation revealed a parietal mass in the left iliac fossa and a pelvic mass; TV: soft vaginal wall and median neck; RT: perception of a haemorrhoidal bulge at noon in the gynecological position and the parameters were soft; the lymph nodes were free;

Elsewhere, there was a soft left mastectomy scar with no sign of locoregional recurrence. The contralateral breast was normal; the other organs and systems were unremarkable.

We suspected abdominal or pelvic metastatic recurrence after complete remission of a left breast ICC initially classified as pT2N1M0. However, a second primary tumor of abdominal or pelvic origin could not be excluded.

Cytology of the ascites fluid was nonsuspicious but lymphocytic.

Abdominal and pelvic CT showed moderate ascites associated with densification and heterogeneity of the uterus and ovary (Figure 3).

Figure 3. Axial section showing uterine and ovarian densification and heterogeneity on CT scan.

The chest X-ray was normal, but there was moderate cardiomegaly with no sign of overload.

Biological examination showed CA 15.3 =375.47 U/ml and CA 125 =600 U/ml (VN ‘35 U/ml). An ultrasound-guided ovarian biopsy was performed, which confirmed the ovarian location of a non-specific infiltrating ductal carcinoma of SBRII grade; on immunohistochemistry (ER-negative, PR negative, and HER2 negative).

Recurrence of metastatic ovarian carcinoma with peritoneal carcinosis following radical treatment of ICC of the left breast initially classified as pT2N1M0 treated by radical surgery, adjuvant chemotherapy, and radiotherapy in a 75-year-old patient with IOMS 2 was retained.

The case was discussed at the PCR for exploratory laparotomy, which did not take place because of the patient’s death. The death occurred 01 week after an emergency admission to MEDISAR Polyclinic; in a situation of multi-visceral failure.

2.3. Clinical Case Nº 3

The patient aged 61, is hypertensive and diabetic, with a history of cesarean section, left oophorectomy in 1992, and lumpectomy of the left breast in 2012, and a family history of 2nd-degree breast cancer (her aunt).

We have no information on the patient's BRCA molecular profile.

Her menarche and first pregnancy were at the age of 15; she has had 3 pregnancies, delivered 2, and aborted 1. She had been menopausal for 11 years. She had never been on oral contraceptives or hormone replacement therapy (HRT).

She consulted the MEDISAR polyclinic for abdominal distension and weight loss. The onset of the disease was eight (8) years ago, marked by the appearance of a nodule located in the upper external quadrant (SEQ) of the left breast. After mammography, she decided to travel to Dakar for treatment, where she underwent excision under general anaesthetic and sentinel node sampling, the histopathological analysis of which concluded that it was an infiltrating ductal adenocarcinoma of grade SBRII. She returned to Donka UCO, where we started adjuvant chemotherapy under the AC75 protocol (4 courses) with good clinical tolerance. Five months after her last course of chemotherapy, she underwent cobalt therapy, which delivered 50Gy on the left breast by 2 opposite tangential beams in 25 sessions with 10Gy superimposed from the 16th session on the tumor bed. The supra-clavicular fossa received 46Gy in 23 sessions using a direct anterior beam. Tolerance was marked by grade II radiodermatitis, especially in the submammary fold, and a cough. She was treated with tamoxifen for 5 years. After these treatments, we monitored her quarterly, six-monthly, and then annually. During the 7 years of monitoring, we noted no locoregional or metastatic recurrence and the CA 15.3 was within normal limits. However, she developed a pruritic rash associated with scratching lesions and was put on Diprostene and Aerius.

Eight years after her diagnosis of breast cancer, she consulted the MEDISAR polyclinic for abdominal distension and weight loss.

The patient had a WHO performance index of 02. The abdomen was enlarged, the umbilicus was protruding, and the flanks were sloping. Palpation revealed a hard pelvic-abdominal mass; the breasts were asymmetric at the expense of the left breast, the site of a radial scar on the axillary extension, associated with thickening of the areolar mammary plate; no associated adenopathies; on TV: the cervix appeared normal; the TR was unremarkable; elsewhere, a soft Pfannenstiel scar was noted.
We suspected abdominal or pelvic metastatic recurrence of an infiltrating ductal adenocarcinoma of the left breast. However, this did not rule out a second primary abdominopelvic tumor. Cytology of the ascites puncture fluid was non-suspicious but lymphocytic.

A thoracic-abdominal-pelvic CT scan showed a moderate amount of pleural fluid effusion, a large number of ascites, a myomatous uterus, and an enlarged and irregular right ovary that looked suspicious (Figures 4, 5).

On biology, CA 15.3=141.63U/ml (VN '35U/ml) and CA125 =184.84 U/ml (VN '35U/ml).

The diagnosis of ovarian metastatic recurrence of a left breast ICC in a 61-year-old patient with a history of oophorectomy, cesarean section, lumpectomy, and 2nd-degree cancer, hypertensive and diabetic with good follow-up on IOMS 02 was accepted.

The PCR recommended exploratory laparotomy. Cardiac assessment by echocardiography was normal, with a systolic ejection fraction of 70% and a regular sinus rhythm on the electrocardiogram, with a heart rate of 93 beats per minute.

The laparotomy performed 10 days after her consultation for abdominal distension revealed peritoneal carcinosis with the aspiration of 6 liters of ascites fluid, an epiploic and greaves cake with absence of the left ovary. We performed an omentectomy and hysterectomy with right adnexectomy (Figure 5). The patient was treated with antibiotics and painkillers.

Pathology confirmed ovarian metastasis of known breast carcinoma, with the following immunohistochemical profile: (CK AE1-AE3, Napsin, and GATA 3) positive and (P53, P16, Ca125, PAX 8, and WT1) negative. The patient died 15 days after the operation in hypovolaemic shock.

3. Discussion

Ovarian cancer is the 5th most common cancer in women. It is the most fatal of all malignant gynecological tumors [9, 10]. Breast cancer is by far the most common gynecological cancer, and its prognosis is directly correlated with the existence of metastases. The liver, skeleton, and lungs are the most common sites of metastasis, while ovarian metastases appear to be rare and less well-known [11].

The discovery of an ovarian mass in a woman with a history of breast cancer raises questions about its secondary or primary origin [12]. According to the literature, the incidence of ovarian metastases from breast cancer is around 20-30%. It seems more than obvious that the discovery of an ovarian mass at a distance from breast cancer is three times more likely to lead to the diagnosis of a primary malignant tumor of the ovary than an ovarian metastasis. In our study, 2/3 of patients presented with ovarian metastasis of breast cancer compared with 1/3 with primary ovarian cancer.

The mean age of patients at diagnosis of ovarian metastasis varies little between studies. In the present study, we found a mean age at diagnosis of 68 years. More interesting to
consider is the time interval between the diagnosis of the primary cancer and that of the ovarian metastasis [13]. This interval varies considerably from one study to another, ranging from 11.5 months for Gagnon et al [14] to 63 months for Bouédec et al [15]. In our study, we found a delay of 96 months between the diagnosis of breast cancer and ovarian metastasis. This result confirms the data in the literature. In general, the time interval between the diagnosis of ovarian metastasis and that of primary cancer seems to be longer for breast cancer than for any other primary site [16]. This could be explained by the fact that residual cancer cells have entered a quiescent phase after an initial phase of intense treatment to escape adjuvant breast cancer therapies. In general, preoperative diagnosis of secondary ovarian tumors is difficult [12]. When they are clinically significant, ovarian metastases are discovered at the stage of peritoneal carcinosis [12], suggestive of multi-visceral involvement.

Depending on the type of breast cancer, infiltrating lobular breast carcinoma shows a tropism for the pelvis and adnexa as a metastatic site compared with other histological types of breast [16]. The probability of occurrence of secondary ovarian lesions is four to five times higher in infiltrating lobular carcinomas than in infiltrating ductal carcinomas [4]. This contrasts with the results of our study: of the two patients who presented with ovarian metastasis, 100% had been previously treated for invasive ductal carcinoma of the breast.

This difference could be explained by the fact that ductal infiltrating carcinoma is the histological type most frequently diagnosed in women in Guinea.

In addition, women diagnosed with breast cancer are likely to have ovarian cancer. The main reason given for this is the discovery of a genomic abnormality, in particular, a BRCA 1 or 2 mutation in 20% of women [17]. In our study, however, we were unable to verify this hypothesis, as there was no oncogenetic test to detect this genetic abnormality. Clinical signs were dominated by abdominal distension indicating the presence of peritoneal carcinosis, ascites, and weight loss.

These signs were found in two of the three patients. Ritta A et al [12] in 2006 found that ascites were more frequent in patients with primary ovarian cancer than in those with secondary ovarian tumors. In contrast to these results, in our study only patients with distant metastatic ovarian recurrence of breast cancer had ascites.

This difference could be explained, on the one hand, by the small size of our sample and, on the other hand, by the clinical polymorphism of ovarian tumors.

In our series, the level of the biological tumor marker CA 125 was higher in patients with metastatic ovarian recurrence after breast cancer than in those with primary ovarian cancer. CA 125 levels were 600 U/ml and 184 U/ml respectively compared with 88.18 U/ml. Ritta A et al [12] stated in their study that serum CA. 125 levels could be equally high in both groups. This hypothesis was confirmed by the results of this study.

We found that serum CA 15.3 levels were even higher in patients with ovarian metastatic recurrence of breast cancer (375.47U/ml and 141.63U/ml).

However, these results must be interpreted with caution due to the lack of sensitivity of most tumor biomarkers. On the other hand, these results suggest that in the presence of a known history of cancer, a solid tumor in the ovaries, and the absence of ascites, the most plausible hypothesis should be that of an ovarian metastatic recurrence of primary cancer, especially as the marker associated with this primary site is elevated.

Anatomopathological examination coupled with immunohistochemistry remains the key element in differential diagnosis. This alone has enabled us to determine the metachronous or metastatic nature of these tumors.

In the present study, one of our patients presenting with a metastatic ovarian tumor had a WT-1-; P53- immunohistochemical profile. Rabban JT et al [18], in a study of risk-reducing salpingo-oophorectomies for ovarian cancers in women with BRCA mutations, examining the differential diagnosis between occult and metastatic primary ovarian carcinoma, concluded that patients with occult primary ovarian carcinoma in contrast to patients with ovarian metastasis due to breast cancer have a WT-1+; P53+ immunohistochemical profile. In addition, the authors pointed out that positive staining for GATA3 may suggest a diagnosis of breast metastasis [18]. This observation was also made in this patient with ovarian metastasis of breast cancer. These results demonstrate the importance of immunohistochemistry in the differential diagnosis of ovarian metastases of breast cancer.

In the case of breast cancer metastasizing to the ovaries, conventional treatment includes surgery to confirm the diagnosis, followed by chemotherapy, hormone therapy, and radiotherapy depending on the patient's symptoms and local and general progression [19, 20]. In our study, two of our patients presented with a secondary ovarian location after breast cancer. One of these patients was scheduled for exploratory laparotomy, but this did not take place because she died. The biopsy carried out on this patient confirmed a non-specific infiltrating ductal carcinoma of grade SBRII, triple negative located in the ovary.

The second patient underwent an exploratory laparotomy during which a hysterectomy with adnexectomy and an omentectomy were performed, with simple post-operative management. However, she died 15 days after surgery in hypovolemic shock.

Anatomopathological examination of the surgical specimen confirmed ovarian metastasis of the known breast carcinoma. Treatment of primary ovarian cancer is based on surgery and chemotherapy. Reference protocols are still dominated by platinum salts and taxanes. In the present study, our patient with a primary ovarian tumor following breast cancer received 12 courses of palliative chemotherapy using the carboplatin-paclitaxel protocol, with a partial clinical response but died 4 months after her last course of chemotherapy with decompensated anemia.

Overall, the prognosis for secondary ovarian cancer is very poor [20].
Among the prognostic factors studied in the literature, the presence of tumor residue after ovarian surgery remains associated with poor survival [21, 22].

Median survival is estimated at 02 years and survival at 05 years is around 18%

Compared with secondary ovarian cancer, primary ovarian tumors also have a poor prognosis, due to their late diagnosis. Their prognosis depends on the FIGO stage, histological type, grade of differentiation, age, general condition of the patient, and the quality of primary cytoreduction, among other factors. The survival rate ranged from 84% for stage I to 22% for stage IV.

4. Conclusion

This study shows the need to include monitoring of gynecological organs in patients treated for breast cancer. These were patients whose BRCA status was unknown. The first case was a second primary cancer, while the other two involved a metastasis of a treated breast cancer. Immunohistochemistry was a valuable aid to diagnosis. In all cases, treatment combining surgery and chemotherapy was complex due to the late diagnosis of the cases. The prognosis was poor.

These cases could be indexes of breast-ovarian syndrome, hence the need to introduce genetic testing in the management of ovarian cancers after breast cancer treatment.

References


