

## Case Report

## Male Breast Cancer: About 05 Cases

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**Abstract:** Male breast cancer is a rare disease (about 1% of breast cancers) with a poor prognosis. The diagnosis is most often late and lesions are treated in advanced stages. The aim of this study was to analyze the clinical, histological, therapeutic and prognostic characteristics of male breast cancer. This was a retrospective study of 05 patients collected in the thoracic surgery department of the Marrakech military hospital. The average age of our patients was 66.2 years. The average consultation time was 11.8 months, and self-care of a breast nodule was the main reason for consultation in 60% of cases. Invasive ductal carcinoma was the predominant histological type in 66.7% of cases. Multimodal therapeutic management consisted of mastectomy followed by adjuvant treatment with chemotherapy, radiotherapy and/or hormone therapy depending on the stage of the tumor and histological characteristics. The hormone dependence of these tumors is proven in 60% of cases. Five-year survival is currently being evaluated. Node invasion, invasion of the dermis and the TNM, clinical stage are factors that significantly influence the occurrence of metastases. None of these risk factors were found to be significant in terms of overall survival.

**Keywords:** Men, breast cancer, prognosis, treatment.

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## INTRODUCTION

Male breast cancer is a rare condition accounting for approximately 1% of all breast cancers and less than 1% of all male nipples [1]. Its incidence has increased markedly over the past 25 years [2].

In Morocco, the incidence of breast cancer in men, according to the two national registers (Rabat Cancer Registry and Greater Casablanca Cancer Registry) is estimated at 0.8-1 [3]. Its etiology remains poorly known, but certain risk factors seem to be incriminated. It is a poorly understood condition in the general public and its diagnosis is often delayed, making the prognosis poor [1, 2]. There are no well codified guidelines for therapeutic management due to the small number of randomized prospective studies.

Treatment is multidisciplinary, involving surgery, radiotherapy and chemotherapy, as well as innovative therapies that improve the overall survival of patients [4].

Through our work we intend to emphasize the epidemiological, etiological, clinical, therapeutic and evolutionary particularities of breast cancer in men, through a retrospective study of 5 observations

collected in the Avicenne Military Hospital of Marrakech.

## PATIENTS AND OBSERVATIONS

## Observation 1

This is a 65-year-old patient, hypertensive on Amlodipine, diabetic on insulin and oral antidiabetics since 2003, followed for benign prostatic hypertrophy under treatment, chronic smoker at a rate of 20 P.A. weaned in 2002 with notion of occasional alcohol consumption.

The onset of the symptomatology dates back to 1 year after her admission with the discovery on autopalpation of a nodule in the right breast progressively increasing in volume without associated pain, redness or nipple discharge.

Clinical examination revealed a breast nodule in the right upper external quadrant, approximately 3cm in size, firm, painless, and mobile in relation to both the deep and superficial planes, associated with a mobile right axillary adenopathy without inflammatory signs.

The rest of the clinical examination was unremarkable.

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Mammography and breast ultrasound revealed a malignant lesion in the upper right breast quadrant classified as ACR 5.

The patient underwent a trocūt biopsy of the breast nodule, revealing an infiltrating ductal carcinoma grade 3 of SBR, with no in situ component.

Immunohistochemistry revealed positive estrogen receptors and HER2 over expression (score 3+).

The extension work-up was negative, and the CA15-3 marker was normal. The tumor was classified as cT2N1M0.

The patient underwent a modified right radical mastectomy with lymph node dissection. The postoperative course was simple.

Pathological examination of the surgical specimen revealed a 2.5 cm long focus of a non-specific grade 3 SBR infiltrating carcinoma with healthy borders and peri-tumoral vascular emboli. Dissection had returned 05 nodes, all of which were unaffected. The tumor was therefore classified as pT2NxM0 (Nx: the lymph node dissection was considered incomplete, bringing back less than 8-10 axillary nodes).

The patient received adjuvant chemotherapy, consisting of 3 courses of FEC100 (5 Fluorouracil, Cyclophosphamide, Epirubicin) and 3 courses of Docetaxel with good tolerance, combined with Trastuzumab. The latter was maintained for 1 year.

As he received radiotherapy to the chest wall and axilla with a dose of 50Gy at a rate of 2Gy/fraction spread over 5 weeks, after a 4-month delay in surgical management. The evolution was marked by the development of radiodermatitis as a complication.

Ten months later, the patient developed lung and then brain metastases, revealed by a dry cough and an intracranial hypertension syndrome.

The patient was put on an adapted chemotherapy, currently still under treatment.

#### **Observation 2:**

The patient was 65 years old, a chronic smoker, with no particular pathological history, and presented about 5 months after his admission with a painless retroareolar swelling of the left breast, progressively increasing in volume, without associated nipple discharge.

Clinical examination revealed on inspection the presence of a budding and crusty areola-nipple lesion surrounded by an erythematous halo; on palpation, it was a retroareolar nodule of about 3cm,

hard consistency, painless, with irregular contours, mobile in relation to the deep plane and fixed in relation to the superficial plane.

The rest of the somatic examination was unremarkable.

Mammography and breast ultrasound revealed a retroareolar malignant image classified as ACR 5.

The patient underwent a non-contributory percutaneous trocūt biopsy.

A surgical biopsy was performed with an extemporaneous examination revealing an infiltrating ductal carcinoma grade 2 of SBR.

The extension work-up, consisting of a thoracic-abdominal-pelvic CT scan and a bone scan, was without abnormalities, while the CA15-3 assay was very high (>100).

The tumor was classified as cT2N0M0.

The patient underwent a modified radical mastectomy with lymph node dissection.

Pathological examination of the surgical specimen revealed a 2.5 cm focus of SBR grade II invasive ductal carcinoma with healthy margins and the presence of vascular emboli. Node dissection yielded 20 nodes of which 3 were invaded.

Immunohistochemical complement revealed positive estrogen receptors, with no HER2 overexpression.

The tumor was therefore classified as pT2N1M0.

The patient received adjuvant chemotherapy consisting of 3 courses of FEC100 and 3 docetaxel, with good tolerance, combined with radiotherapy, after a delay of 6 months from surgery, of 50GY to the chest wall and axillary fossa. Hormone therapy with anti-estrogens (Tamoxifen) for 5 years.

The evolution was marked by the appearance of radiodermatitis as well as a radiation pneumonitis that appeared 6 months after HTR.

#### **Observation 3**

The patient was 56 years old, a chronic smoker, with no particular pathological history, and presented with a painless right breast mass, progressively increasing in volume, which had been evolving for about a year and a half without any other associated signs, in a context of conservation of the general state.

Clinical examination revealed a huge right breast mass of about 20 cm long, firm, painless, mobile in relation to the superficial plane and fixed in relation to the deep plane, with telangiectasias on the surface, without inflammatory signs opposite. The lymph nodes were free.

The rest of the clinical examination was unremarkable.

A chest CT scan was performed showing a huge right parietal tumor process of about 18cm long axis, which seemed to grow from the pectoral muscles, making rhabdomyosarcoma the first possibility.

A thoracic-abdominal-pelvic CT scan was performed to assess the extent of the disease, but no abnormalities were found.

The tumor was classified as cT3N0M0.

The patient underwent a right mastectomy without lymph node dissection, with immediate reconstruction using a dorsal is major muscle flap with simple postoperative follow-up.

Pathological examination of the surgical specimen revealed a myxoid liposarcoma invading the striated muscle structures in the periphery.

The patient underwent adjuvant chemotherapy with good progression in 06 months.

#### Observation 4

This is a 68-year-old patient, chronic smoker, with no particular pathological history, who presented with a painless right breast swelling that had been evolving for 1 year, progressively increasing in volume, in a context of altered general condition (anorexia, weight loss of 5kg over a period of 3 months).

Clinical examination revealed an ulcerating mass in the right breast (Figures 3 and 4), approximately 9 cm in length, fixed in relation to the deep plane of the chest wall, with inflammatory signs opposite.

Examination of the lymph nodes revealed a mobile homolateral axillary adenopathy.



**Figure 1: Ulcerative mass of the right breast**

A thoracic CT scan showed a tumor process measuring 8x9cm in diameter, a surgical biopsy was performed revealing a proliferation of spindle cells with atypical mitoses (9-10 per field) of pectoralis major muscle. On immunohistochemical complement, the staining was positive for Ki67 intensely and diffusely, as well as for AML (smooth muscle actin) and H-caldesmone, and negative for PS100 and for cytokeratins (AE1/AE3). The diagnosis of leiomyosarcoma was made.

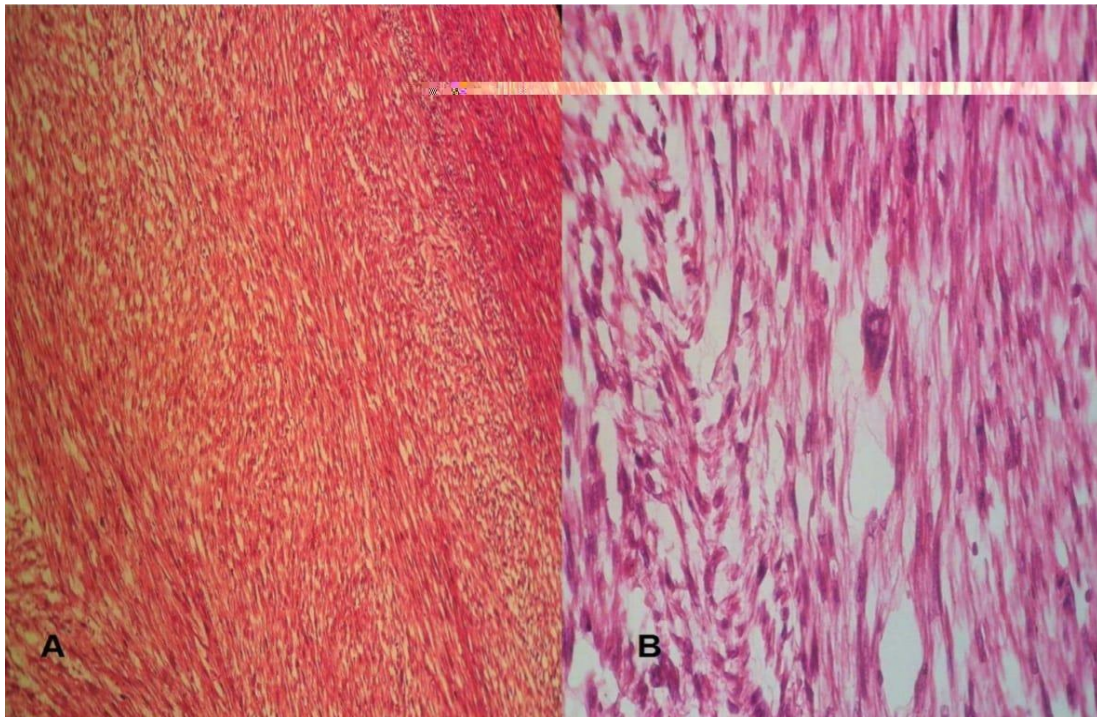
The extension work-up, consisting of a body scan and a bone scan, was without abnormalities.

The patient underwent a radical mastectomy with total resection of both pectoral muscles and lymph node dissection.

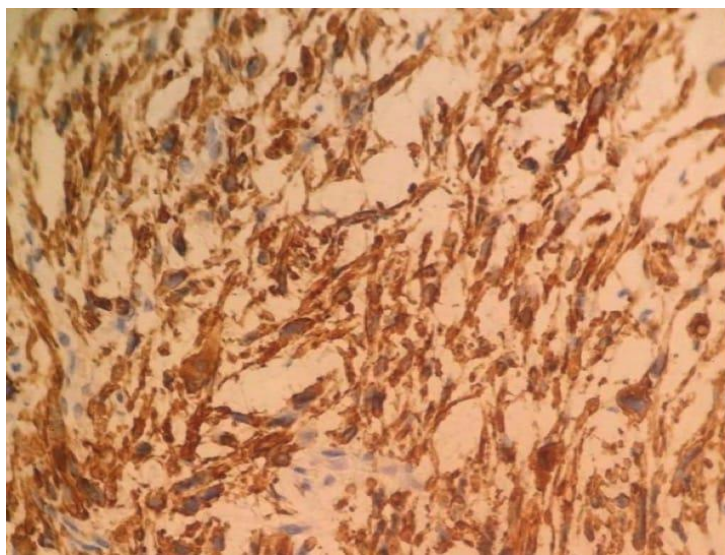
Immediate reconstruction surgery was performed using a dorsalis major muscle flap.

Pathological examination of the surgical specimen revealed a necrotic tumor measuring 11x8x10 cm in diameter with healthy surgical margins (3 mm deep and 3 cm at the lateral margins) and confirmed the diagnosis of FNCLCC grade II leiomyosarcoma.

The lymph node dissection had returned 21 lymph nodes, all of which were unharmed.



**Figure 2: HE staining at high magnification reveals spindle cells with encapsulated nuclei. A: x40 B: x100**



**Figure 3: Immunohistochemical analysis showing staining for H-caldesmon (x40)**

The patient received adjuvant radiotherapy to the tumor bed and adjacent chest wall of 50 Gy in 25 fractions of 2 Gy, with five fractions per week.

After a close follow-up, we did not detect any relapse, either local recurrence or distant metastasis, over the course of 03 years.

#### **Observation 5**

The patient is 77 years old, chronic smoker, diabetic on insulin since 2019, followed by Alzheimer's disease with treatment, operated on for appendicular peritonitis in 2019.

He presented to our clinic with a painless right breast swelling (Figure 3) that had been progressively increasing in size for 1 year, followed by nipple retraction 6 months later, with no associated pain, redness or nipple discharge.

Clinical examination revealed a retraction of the nipple (Figure 4) associated with a palpable nodule in the upper-external quadrant of the right breast, approximately 3cm in size, hard, irregular in outline, painless, mobile in relation to the deep plane and fixed in relation to the superficial plane, with no inflammatory signs opposite.

The lymph node examination revealed a fixed homolateral axillary adenopathy. The tumor was therefore classified as cT2N2Mx.

The breast ultrasound showed a para-areolar nodule (Figure 5) on the right breast with irregular contours and a malignant appearance, associated with a right axillary adenopathy of 17 mm in length.

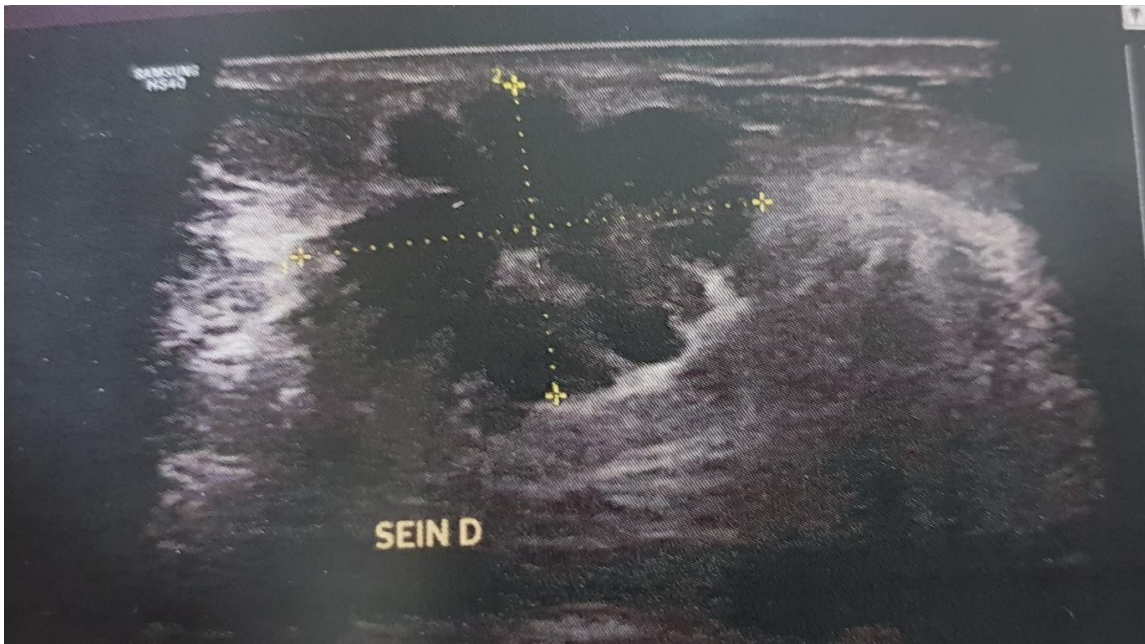


Figure 4: Image of a hypochoic formation with irregular contours in the right breast in the paraareolar region



Figure 5: Hypochoic axillary adenopathy measuring 1.73cm

A mastectomy with lymph node dissection was performed, with simple post-operative follow-up

Pathological study of the surgical specimen showed an infiltrating ductal carcinoma of SBR grade II, measuring 3cm in long axis, with infiltration of the nipple, presence of an intermediate grade ductal in situ component, and gynecomastia lesion in the periphery of the tumor.

The surgical margins were healthy, with the presence of vascular emboli and perineural meshwork. The lymph node dissection had brought back 16 axillary nodes, 8 of which were invaded without capsular rupture.

The tumor was therefore classified as pT2N2aMx.

The immunohistochemical study revealed positive progesterone and estrogen receptors without HER2 expression.

The extension workup was negative; the patient is currently undergoing adjuvant chemotherapy with good progression.

## DISCUSSION

Male breast cancer is a rare disease. Its prevalence is one per 100,000 individuals and it represents less than 1% of breast cancers and less than 1% of all male nipples [1, 2]. The incidence of this disease appears to be relatively stable in Europe [1], but Giordano *et al* show an increase of 26% between 1973 and 1998 in the United States.

The first description dates back to 1307 and was made by an English surgeon, John of Arderne.

The average age of diagnosis of breast cancer is generally higher in men than in women [5].

The average age of discovery of breast cancer in men is 67 years, which is five years older than the age of discovery of breast cancer in women (10) with extremes ranging from 50 to 93 years [6].

In our series the mean age of onset was 66.2 years with extremes between 56 and 77 years. This is in agreement with the literature.

The etiopathogenesis of male breast cancer remains poorly defined, however, many risk factors seem to be incriminated. Obesity by aromatization of androgens and ethylic cirrhosis by elevation of sex steroid binding globulin cause a state of hyperoestrogenism [7]. Testicular abnormalities such as testicular ectopia, orchitis, orchiectomy, congenital inguinal hernias and infertility are factors associated with a high risk of breast cancer. Umbilical breasts, history of breast trauma and transsexuality (including surgical and chemical castration) appear to be involved [7-8]. Hypogonadism, present in Klinefelter's syndrome, is a classically accepted risk factor (20-50 fold relative risk compared to a man without genetic abnormalities) but this predisposition is also thought to be explained by exogenous supply of testosterone, converted to estrogen in peripheral fat [7].

Men with a family history of female breast cancer are 2.5 times more likely to develop breast cancer. Exposure to electromagnetic fields affects pineal gland activity with a decrease in melatonin (hormone with antiestrogenic action) levels [4, 9, 10]. A history of radiation (latency period of 20 to 30 years) and exposure to high temperatures [7] have also been incriminated and finally, regular alcohol consumption has also been found [7, 9, 11]. However, idiopathic or drug-induced gynecomastia has not been implicated in the occurrence of this condition [4, 7, 12].

The main genetic factors associated with an increased risk of breast cancer in men include BRCA2 mutations, which are thought to be responsible for the majority of hereditary breast cancers in men, BRCA1 mutations are present in only 10-16% of patients without a family history [13 14, 15]. BRCA2 mutations are more common in male breast cancer and are estimated to be present in 4- 16% [16]. It is because of the prevalence of these mutations in male breast cancer that genetic counseling should be offered. The cumulative risk of male breast cancer is 6.3% at age 70 [8]. The percentage of BRCA2 mutation expression in male breast cancer varies between populations (3.6-40%) reflecting genetic differences between populations [17, 18]. Cowden syndrome is an autosomal dominant disease characterized by the development of multiple hamartomas associated with the germline mutation of the tumor suppressor PTEN gene, located at 10q23. It causes breast cancer in both men and women [7, 19]. The CHEK2 mutation, which is a kinase involved in DNA repair, CHEK2\*1100delC, has been implicated in the development of male breast cancer, Klinefelter syndrome and a family history of breast cancer. Suspected genetic factors include AR gene mutations, CYP17 polymorphism, Cowden syndrome and CHEK2.

The delay between the first symptoms and the diagnosis is later than in women [15]. In our series, the average delay was 11.8 months, with extremes ranging from 5 to 18 months. It can be assumed that this delay is explained by the lack of knowledge of the disease and the denial of this condition, which is considered exclusively female.

In our series, 03 of our patients consulted for a retro nipple nodule. Male breast cancer is most often found in the left breast [20-22].

For Rbaibi *et al.*, (87) and Seitzinger *et al.*, [23] the incidence of male breast cancer is higher in the right breast. While bilateral forms are unusual (0 to 1.4%).

In our series, right breast involvement was significantly higher at 80% compared to 20% for the left breast, and no bilateral involvement was observed. The sensitivity and specificity of mammography in the diagnosis of male breast cancer are 90 and 92% respectively [16]. Breast ultrasound complements mammography and provides information on lymph node status. Imaging is systematically complemented by a micro biopsy. Staging is always based on the TNM classification. As in women, the extension work-up includes the same examinations (chest x-ray, liver ultrasound, bone scan and CA 15-3 assay) [15-17].

The most common histological type Ductal carcinoma in situ (DCIS) accounts for 10% of male breast cancers [24]. Lobular carcinoma in situ is rare

due to the absence of terminal lobules ; but has been described in association with invasive lobular carcinoma in male breast cancer [19]. In our series, lobular carcinoma in situ was not described on the resection specimens, whereas ductal carcinoma in situ was found in only one patient. With regard to invasive carcinomas, the histological types are similar for both sexes but with a different frequency [24]. Data from the surveillance of 2000 patients in the SEER (Surveillance, Epidemiology, and End Results cancer registry) showed that 93.7% of male breast cancers are ductal or unclassified, 2.6% are papillary, 1.8% are mucinous and only 1.5% are lobular [24]. In our series ductal carcinoma is the predominant one representing 60% of cases.

Two patients in our series, i.e. 40%, had presented with breast sarcoma.

There is a high degree of hormone dependence in these tumors. Approximately 90% express estrogen receptors and 81% express progesterone receptors [24]. In our series, hormone receptors were strongly positive in all cases. The level of hormone receptor expression in male breast cancer is significantly higher than in women and increases, as in women, with the age of the patient [24, 26]. A recent study on a series of 75 patients showed that 5% of male breast cancers have her2-neu overexpression [27]. The role of androgen receptors is unclear and does not affect the prognosis of male breast cancer [28, 29]. It appears to have a worse prognosis than in women. Tumour size and lymph node involvement are two important prognostic factors in male breast cancer [24]. Men with a tumour of 2-5 cm in diameter have a 40% higher risk of death than men with a tumour of less than 2 cm in maximum diameter. We did not find any information in the literature about the stage of discovery of breast cancer in men compared to the stage of diagnosis in women. However, at the same stage, survival was the same. In the case of node involvement, there is a 50% higher risk of death than in the case of nodes without metastases.

In univariate analysis, hormone receptor negativity and tumor grade are associated with poor prognosis for survival [24, 14]. Male breast cancer due to a BRCA2 mutation occurs earlier and with a poorer prognosis [13, 14]. In general, the prognosis for female and male breast cancer patients is similar [2-4, 13-15]. The treatment strategy for the management of cancer in men is similar to that for women [9, 10]. In the early stage, most men are treated with modified radical mastectomy combined with axillary dissection or selective lymphadenectomy [30-33]. The small size of the mammary gland makes it difficult to move to healthy margins. Therefore, lumpectomy is not recommended [1]. Thus, conservative surgical treatment has no place in the treatment of male breast cancer, on the one hand, because of the small size of the breast and, on the other, because of the easy acceptance

of mastectomy. On the other hand, all other treatments, surgical (axillary or sentinel lymph node), radiotherapy, chemotherapy, hormone therapy (tamoxifen or anti-aromatase) and biotherapy (trastuzumab) can be part of the therapeutic arsenal. Axillary dissection is still necessary [12]. Axillary lymph node dissection is complicated by disabling upper limb lymphoedema in 10-25% of cases. Selective lymphadenectomy has recently been evaluated in male breast cancer [34, 35]. Given the rarity of this disease, the sensitivity and specificity of the sentinel lymph node have not been evaluated but several series have been published establishing the feasibility of the technique in this indication [36-37]. Radiotherapy is more often indicated in men after mastectomy than in women because of the frequency of nipple or skin involvement [38]. Radiotherapy prevents locoregional recurrence but studies have not shown a difference in survival [38]. In our series, the indication for radiotherapy was retained in 3 of our patients. There is little information on the efficacy of adjuvant chemotherapy in male breast cancer. Only one prospective study has been published for this purpose in 24 men who received CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy with a survival rate of over 80% at five years, and significantly greater than in a similar cohort [39]. Retrospective series have shown a decreased risk of recurrence in patients [12]. Often the same chemotherapy protocols are used for women. At the University of Texas M.D.-Anderson Cancer Center [41], chemotherapy is indicated if the tumor size is greater than 1 cm and if there is lymph node involvement. Anthracyclines are proposed alone if the lymph nodes are free and in combination with taxanes in case of lymph node involvement. Hormone therapy is indicated if receptors are present [4, 41]. Retrospective studies evaluating adjuvant tamoxifen have shown a reduced risk of recurrence and death. The toxicity of tamoxifen in humans has not been studied. Some studies have described intolerance, venous thrombosis, decreased libido, and mood disorders and hot flushes [42]. With regard to antiaromatases, only one series has been published on five patients with metastatic disease but with no objective response [43]. Two cases have recently been reported in patients treated with letrozole with a significant decrease in tumor mass [44, 45] but further investigations are needed to determine the efficacy of antiaromatases in humans.

To date, there is insufficient data to recommend antiaromatous drugs as adjuvant therapy in humans.

In the metastatic stage: the therapeutic attitude is the same as in women. Hormone therapy is often indicated due to frequent receptor positivity. Farrow and Adair [16] described a case of male breast cancer that regressed after orchiectomy. Historically, orchiectomy, adrenalectomy and hypophysectomy have been performed to control metastatic breast cancer but

are now replaced by hormone therapy. Tamoxifen is the drug of choice with a 50% response rate [15- 18]. LH-RH agonists have also been used with or without anti androgens and have proven to be effective in metastatic breast cancer in men [17]. In our series, only one metastatic patient received first-line hormonal therapy such as tamoxifen. Chemotherapy is appropriate for patients with negative hormone receptors or in cases of resistance to first-line hormone therapy [17, 18]. The efficacy of trastuzumab in overexpressing men is unproven but should be tried in metastatic men with HER-2 overexpression according to Volm *et al.*, [17]. Palliative chemotherapy may be indicated in cases of rapid disease progression [17, 18]. The 5 and 10 year overall survival of male breast cancer is around 60 and 40%.

## CONCLUSION

Breast cancer in men is a rare disease. The risk factors are multiple and varied. The diagnosis is made at a later age than in women and at a more advanced stage, which constitutes a prognostic factor. The number of invading lymph nodes and the size of the tumor are also powerful prognostic factors. The other pejorative prognostic factor is the advanced age at diagnosis, especially in the presence of co-morbidities, which could limit the choices and therapeutic possibilities, hence the interest in conducting larger-scale prospective studies to improve the management and prognosis of this condition.

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