Male breast cancer in central Tunisia: A retrospective case-series

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Background

Male breast cancer (Mbc) represents worldwide less than 1% of malignancies in men and 1% of breast carcinomas. Its incidence has increased over the last four decades, but remains still very low compared to breast cancer in women (2). Mbc has a poor prognosis compared to female breast cancer. This is due to the higher rate of advanced stages at presentation and to the lack of clear therapeutic strategies. Because of the disease rarity, treatment recommendations for Mbc have been extrapolated from results of trials in female patients.

Our objective was to study the clinical, para clinical, histopathological and therapeutic characteristics of patients with Mbc and to assess the survival prognostic factors in a 15-year case series treated in central Tunisia.

Patients and Methods

We conducted a retrospective review of Mbc cases collected in the oncology department of Farhat Hached public hospital in Sousse (Tunisia) over a period of fifteen years (January 1996 to December 2010). The diagnosis of breast cancer was confirmed by histopathological study for each patient. Results of Scraff-Bloom-Richardson grading (SBR) and hormonal receptor status results were obtained when available.

The data analysis including survival curves were conducted with the SPSS software.

Results

From January 1996 to December 2010, 36 cases of male breast cancer (Mbc) were diagnosed in our institution. The mean age at diagnosis was 64 years (range 34-89 years), with 66% of patients aged between 50 and 80 years. Personal medical history of our patients is presented in table 1.

Five patients had a familial cancer history: two cases of female breast cancer, two cases of lung cancer and one case of squamous cell skin carcinoma. No patient had a history of another cancer, especially any history of breast cancer.

Breast tumefaction was the presenting sign common to all patients, followed by breast pain in 15 cases (41.7%) and enlarged axillary lymph nodes in 14 cases (39%). The right breast was more frequently affected than the left one (58%) with no case of bilateral cancer. The retro nipple localization was most frequent (66.7%). The tumor size, as noted in the first examination, ranged from 1 to 10 cm with a mean of 4 cm. Eleven percent of cases had a tumor measuring less than 2 cm.

Radiological diagnosis was made by mammography and/or breast ultrasounds in nineteen patients who had a solitary nodular opacity and two who had multifocal lesions. Patients' characteristics are summarized in table 2. TNM staging was made using X rays, abdominal ultrasounds and bone scintigraphy. Fifty-five percent of patients had a T4 tumor at initial examination. Sixty-eight percent had not axillary lymph node involvement (N0), 20% had movable axillary nodes (N1) and 12% had fixed nodes (N2). Eight patients (22%) had metastatic disease (stage IV): 7 cases of metastases to bone, 3 to lung, 2 to liver and 1 to skin. Thirty-five patients had a ductal carcinoma (97%) and 1 patient a mucinous type. SBR grading was performed in 35 patients; 8% had SBR I tumor, 67% had SBR II tumor and 22% had SBR III tumor.

A total of 32 patients underwent surgery (89%): 25 had a primary surgery (78%) and 7 had a secondary surgery after neoadjuvant chemotherapy. The majority (31 patients) had a radical mastectomy with axillary node clearance (ANC); one patient had a conservative surgery with ANC.

Chemotherapy was given in 31 cases: in adjuvant settings for 19 patients and in neo adjuvant settings for 7 patients. Five patients received palliative chemotherapy. The chemotherapy was mainly based on anthracyclines. Seventeen patients received FAC schedules, 11 received FEC schedules and 3 received CMF schedules (11,12). Twenty-four patients (67%) received adjuvant radiotherapy following chemotherapy in all cases. Hormonal therapy was given to 27 patients, all with tamoxifen.

Overall survival (OS) was on average 54 months with a median survival of 60 months. Two-year and five-year survival rates were respectively 70% and 44 %.(Fig 1: overall survival curve). Disease free survival (DFS) was on average 70.5 months with a median survival of 72 months. Two-year and six-year DFS rates were respectively 73.6% and 37% (Fig2: DFS curve). Survival was significantly better in patients with smaller tumor size (< 2 cm) compared to patients with tumors measuring more than 2 cm (p=0.003), this was also true for patients with lower stage tumors (stage T1 and T2) compared to patients

with higher stage tumors (p=0.006) (Fig 3). Hormone receptor positivity was significantly associated with a better survival (p=0.03) (Fig 4). Initially non metastatic patients had a significantly better survival compared to those with metastases (p=0.03). Patients aged less than 65 years had a better survival than older ones (p=0.005). Patients with no clinical axillary lymph nodes (N0) had better survival than patients with clinical identifiable lymph nodes (N1 and N2) but without reaching strict statistical significance (p=0.08). There was no statistical difference in survival between patients having histological confirmed axillary lymph node metastasis (pN1) and patients with negative nodes (pN0) (p=0.8). Similarly, the histopathological characteristics had no impact on survival.

Discussion

Male breast cancer is rare. According to the Tunisian Center Cancer Registry, Mbc incidence between 1998 and 2007 has remained about 0.7 cases per 100.000 per year. In Tunisia, Mbc represents 1% of malignancies in men and 1.6% of all breast cancers, which is concordant with Mbc situation worldwide in general, and in the Maghreb countries such as Morocco (0.97%). The relative proportion of Mbc among cancers in men is much more important in some sub Saharan countries such as Uganda and Zambia (5% and 15% respectively), where cervical cancers ranked in the leading position for women. This uncommon association led some researchers to hypothesize that since cervical cancer is for most a consequence of a sexually transmitted disease, then possibly a STD may be at the origin of Mbc in the same region (13).

Mbc has increased worldwide by 26% in the last three decades, in parallel to 52% increase in women breast cancer in the same period (1). This is mainly explained by the elongation of the average age worldwide, although Mbc is considered as cancer of the elderly. A familial history of breast cancer, like in female breast cancer, increases the risk of developing a breast neoplasm with a relative risk of 2.5 (3,4). Twenty percent of men with breast cancer have a familial Mbc history in a first degree parent (3). A personal history of breast cancer in one side multiplies by 20 the risk of developing a cancer in the opposite breast (4). Some genetic syndromes are associated in 5% of cases with breast cancer such as Klinefelter syndrome, Cowden syndrome and BRCA1 or BRCA2 mutations. None of these syndromes were found in our patients. Some endocrine anomalies have been suggested as risk factors for Mbc. They include: cryptorchidism, testicular ectopia, orchidectomy and congenital inguinal hernia. In our series, only one case had been operated for inguinal hernia. Gynecomastia has been suggested as Mbc risk factor. In some series, the gynecomastia-Mbc association reaches 60%.

Breast tumefaction is the most frequent clinical sign at diagnosis, occurring in 93.5% of Mbc (5). It is generally noticed by the patient himself. The breast tumefaction is rarely painful (less than 5% of cases) and inflammatory signs are generally absent (less than 2%). Other less frequent clinical signs can be seen in Mbc such as mammary ulceration (6-17%), mammary retraction (9%) and nipple bloody discharge (4-20%) which is correlated with a malign breast disease in 75% of cases (5,6).

The utility of mammography in Mbc is debated because it does not provide, generally, supplementary information relative to clinical findings. The main advantage of breast ultrasounds is to allow the performance of fine needle aspiration cytology and core biopsies, which remain the final diagnostic tests.

More than 85–90% of Mbc are of the invasive ductal type because the male breast normally contains only ducts (6). Thus, lobular type is extremely rare. Other histological subtypes can be seen (tubular, mucinous and papillary). Ductal carcinoma in situ (DCIS) is relatively rare in breast tumors in men (1-10% of cases) compared to women. In a previous Tunisian study about 123 cases of Mbc, 92% of patients had ductal carcinoma. In our series, almost all patients had a ductal carcinoma. The tumor histopathological grade according to the SBR grading system is a predictive factor of chemo sensitivity and tumor aggressiveness. The distribution of Mbc on SBR grades (grades I, II and III) is comparable to female cancers. Aldhiab et al. found SBR II and III tumors in 81.5% of Mbc.

In Mbc, tumor size was identified as an independent survival prognostic factor: the 5-year survival is 94% in tumors less than 1 cm, 80% in tumors 1-4 cm 80% and 40% in tumors more than 4 cm 40% (5). In our series, survival was significantly better in patients having a tumor size less than 2 cm. Axillary lymph node involvement is a very important prognostic factor of survival and replase and is decisive for adjuvant treatment modalities (6). In previous series, the rate of axillary lymph node metastases ranges from 35 to 75%. This rate is dependent on tumor size: about 35% for tumors measuring less than 2 cm and reaching 75% for those measuring more than 2 cm. In the Tunisian series of Aldhiab et al. the rate of axillary positive lymph nodes was 65%. As in breast cancer in women, lymph node involvement is a very important prognostic factor (5). The overall 5-year survival is estimated to be 85% when there is no lymph node involvement and 57% when lymph nodes are involved.

Mbc is more hormone dependent than in women (7). When comparing hormonal receptors in breast cancer between two sexes, breast cancer in men expresses estrogen receptors (ER) in 65-93% of cases and progesterone receptors (PR) in 73-92% of cases; while breast cancer in women expresses ER in 77% and PR in 69%. The tumor hormone receptors positivity is not influenced by age like in woman breast tumors (5,7). In most Mbc reports, the hormone receptors status does not seem to influence survival. This can be due to wide HR positivity in Mbc so that it cannot emerge as a survival factor. In our series, HR positivity was significantly associated with better survival. This is probably explained by the relative balance between positive and negative HR tumors.

The C-Erb-B2 status is less studied in men compared to woman and the effect of trastuzumab therapy is not known. The largest study, reported by Rudlowski et al. showed a C-Erb-B2 positivity in 15 of 99 (15).

In staging Mbc, T4 stage is more frequently found than in female breast cancers. This is due to the small volume of male breast, so that the tumor quickly expands to the chest wall or the breast upper skin with, in some cases, inflammatory signs. A T4 stage tumor or an N2 node status can indicate neoadjuvant chemotherapy before surgical resection.

Most frequent breast cancer metastases are to bone, lung, pleural tissue, liver, peripheral lymph nodes and skin (4). The 5-year survival is significantly better in non metastatic patients compared to metastatic ones, in this series as in other reports (3,4). As Mbc is very rare, its management is of Mbc is guided by breast cancer therapeutic approaches in women, in which surgery remains the backbone, especially in absence of metastases (4,5). Axillary node dissection is an important component of therapy; men who do not receive it tend to have poorer outcomes with 10 times more risk of loco regional relapse (5). Radiation therapy is an important component in local treatment of breast cancer, generally indicated after conservative surgery, positive resection margins or high risk breast carcinomas (high SBR grade, positive axillary lymph nodes, capsular rupture, lymph vascular invasion…) (8,9). Adjuvant radiation therapy improves the relapse free-survival, mainly in high risk tumors (10), but its impact on survival is still not proved. Anuradha et al. had demonstrated in a retrospective study of 44 Mbc cases that post-mastectomy radiation therapy is useless in small and early stage Mbc while it is associated with an improved replase-free survival in high risk tumors (10). Men tend to be treated more often with radiation therapy

than women due to the frequent tumor extension to skin and/or the chest wall. Mbc is sensitive to chemotherapy and indications are again guided by woman breast cancer guidelines and recommendations. One prospective study conducted by Bagley et al. in the National Cancer Institute showed a 5-year survival rate of more than 80% in patients with stage II breast cancer treated with adjuvant CMF chemotherapy. In many other retrospective studies, adjuvant chemotherapy was associated with a reduced risk of relapse and death related to disease. Sharon et al. founded that adjuvant chemotherapy was correlated to 43% decreased risk of death (7). In metastatic and neoadjuvant settings and in the absence of response to hormone therapy, a 13% objective response rate can be achieved with fluorouracil mono chemotherapy, whereas 67% objective response can be reached with an anthracycline-based chemotherapy (FAC and FEC protocols). As Mbc is often HR positive, there is clear evidence that men may benefit from the use of hormone therapy. The efficacy of tamoxifen as a treatment of Mbc is proven in patients with locally advanced and metastatic disease with 25 to 80% of objective response rate (5). Tamoxifen was also associated with an overall survival gain (5-year survival with tamoxifen: 44-61%). Hormone therapy with tamoxifen can be considered actually as a standard treatment for stage IV male breast cancers (7). One series reported that men had some difficulties tolerating tamoxifen. Aromatase inhibitors are new hormone therapy drugs which proved a highest efficacy in adjuvant and metastatic treatment of post menopausal woman breast cancer. Their use is now standard in adjuvant setting, mainly in the high risk groups. They have rarely been used in Mbc and their therapeutic role is not established. Probably, the biggest series, reported by Giordano et al, studied the activity of anastrozole in 5 patients with metastatic Mbc refractory to tamoxifen in which there were 3 cases of disease stability (14).

Conclusion

Male breast cancer shares many similarities with female breast cancer but with some differences mainly in outcome and treatment response. Mbc occurs in older patients compared to woman and is generally diagnosed at advanced disease stages. Chemotherapy and post-mastectomy radiation therapy in Mbc are actually guided by woman breast cancer guidelines and recommendations. As Mbc frequently expresses hormone receptors, hormonal therapy mainly with tamoxifen proved its efficacy in both adjuvant and metastatic settings. Future studies should focus on disease biology to help understanding male breast cancer carcinogenesis and to optimize Mbc management.

Tables

Table 1: Personal and medical history of male breast cancer cases in central Tunisia (1996-2010) (N=36)

Breast disease	4 cases	- 3 cases with gynecomastia - 1 case with intragalactophoric papillomatosis
Hypertension	6 cases	
Diabetes	3 cases	
Cardiac disease	2 cases	Auricular arrhythmia
Asthma	1 case	
Surgical intervention	2 cases	-1 operated for prostatic adenoma -1 operated for inguinal hernia
Smoking	12 cases	
Alcohol	4 cases	
Obesity	3 cases	

Table 2: Male breast cancer histological characteristics in central Tunisia (1996-2010) (N=36)

Histological subtype		
Infiltrating ductal carcinoma	35	97 %
Mucinous carcinoma	1	3 %
SBR grading		
SBR I	3	8.3 %
SBR II	23	66.7 %
SBR III	8	22.2 %
Hormonal receptor status		
Positive	21	62 %
Negative	13	38 %
Axillary lymph node involvement		
Negative	14	43.7 %
Positive nodes	11	34.3 %
> 4 positive nodes	7	22 %
Capsular rupture		
Yes	7	22 %
No	25	78 %
Lymph vascular space invasion		
Yes	9	28 %
No	23	72 %
Her2-neu status	no	No
Disease stage	(n=36)	
stage I	3	8.3 %
stage II	12	33.3 %
stage III	13	36.1 %
stage IV	8	22.2 %

Figures

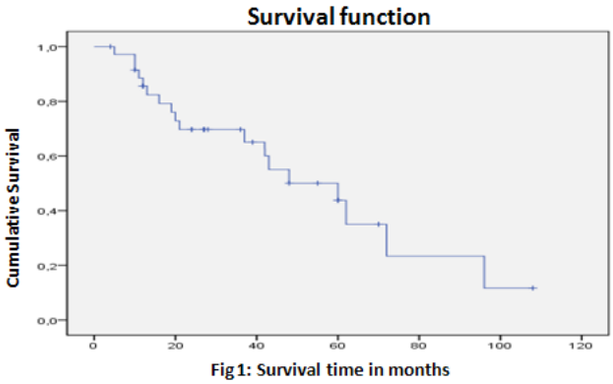

Fig 1 : Overall survival in Mbc population

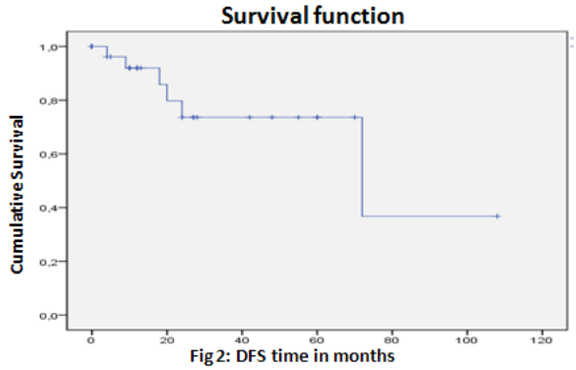

Fig 2 : Disease-free survival in Mbc population

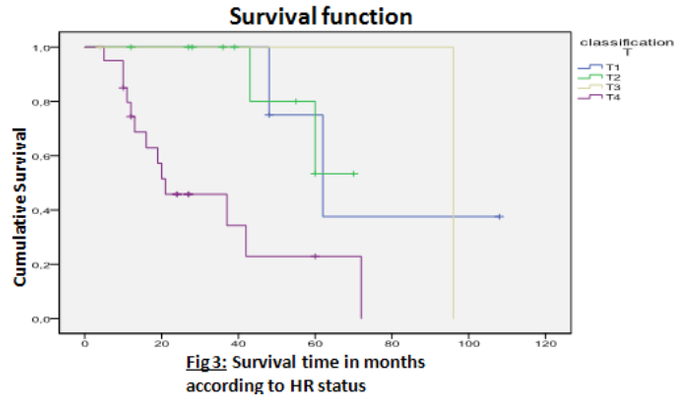

Fig 3 : Survival according to local tumor extension (T stage)

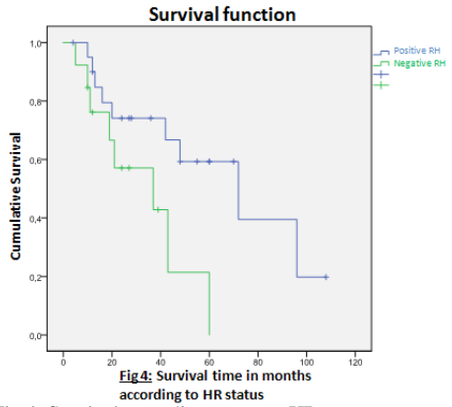

Fig 4: Survival according to tumor HR status

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