BREAST CANCER IN A NIGERIAN COHORT: HISTOPATHOLOGY, IMMUNOHISTOCHEMICAL PROFILE AND SURVIVAL

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Abstract

Aims: The aim was to describe the histological and immunohistochemical characteristics of breast cancer in a Nigerian cohort and correlate the findings with the clinical outcome of management.

Methods and results: The histology of 89 breast cancers was reviewed. Immunohistochemistry (IHC) for estrogen receptor (ER) and Her2/neu was done on 73 cases and progesterone receptor (PR) on 67cases.

Age ranged from 22-82 years (mean = 48±12.3). Invasive ductal carcinoma of no special type (NOS) was the commonest histological variant. Sixty two cases (69.7%) were grade III tumours. IHC was negative for ER in 62%, PR 79%. Her2/neu over-expression was seen in only 4%. About 53% (31/58) of the tumours were negative for all the three markers. At presentation, 68.2% of the patients had stage III and stage IV disease. After 5 years of follow up, 20% of the ER/PR positive patients were dead, 10% had local recurrences and 70% were lost to follow-up. Among the triple negative patients, 50% were alive and well with no recurrence, 20% were dead and 30% were lost to follow-up. All the patients with Her2 positive tumours were dead within 1-2 years.

Conclusion: Our data suggest that breast cancer in Nigeria occurs at younger age, is of high histological grade and is more likely to be triple negative. Clinical outcome tends to be good among the triple negative patients with early stage disease.

Key Words: Breast cancer, Histopathology, Immunohistochemistry profile and Survival.

Introduction

Breast cancer is the commonest malignancy in Nigerian women with an increasing incidence, high mortality rate, late presentation and an earlier age of occurrence compared to other populations[1]. Traditional factors known to predict the behaviour and management of breast cancer worldwide include tumour size, lymph node involvement, and distant metastasis[2]. However, the full picture of the behavioural pattern of breast cancer in Nigerian women remains unclear. For example, few patients who present quite early succumb to the disease while even among the usual late presenters, a distinct pattern has not been linked to the known histological predictive factors[3].

The use of immunohistochemistry to further characterize breast cancer globally has introduced a new dimension to our knowledge of the disease. Breast cancer can no longer be regarded as a single entity and morphological features alone cannot completely predict the behaviour of breast cancer[4]. The three immunohistochemical markers currently in routine diagnostic use in most countries are estrogen receptor (ERα), progesterone receptor (PR) and Her2[5]. These markers determine which tumours are likely to respond to hormonal therapy and Herceptin treatment[6].

The aim of this study was to analyse the histological and immunohistochemical profile of breast cancer in a Nigerian cohort and correlate the findings with the clinical outcome where available.

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Materials and Methods

Cases of invasive breast cancer seen at Obafemi Awolowo Teaching Hospital Ile- Ife Nigeria between 2004 and 2006 were identified. Histological review was performed on sections from the paraffin wax archived materials which were samples taken from these breast cancer cases. This was done following the guidelines of the Royal College of Pathologists (RCPath 2005)[6]. All cases were graded following the RCPath guidelines. Other relevant histological and clinical follow up data were extracted from histological request forms, histological reports and case notes.

Immunohistochemistry

Immunohistochemical staining for estrogen receptor (ERa), progesterone receptor (PR) and Her2/neu were carried out retrospectively on sections

from archived blocks. Dual In-situ Hybridization (ISH) was carried out on all cases with equivocal Her2/neu scores using automated Ventana machine. They were subsequently upgraded to overexpression or downgraded to negative.

Treatment and follow up data were extracted from the case notes. Information related to the clinical outcome that were extracted from the case notes included clinical stage of presentation, response to chemotherapy, recurrence after surgery, disease-free survival and overall survival duration.

The results obtained were analysed using Statistical Package for Social Sciences version 15 for windows.

Results

A total of 89 cases of invasive breast cancer seen at Obafemi Awolowo Teaching Hospital, Ile-Ife, Nigeria between 2004 and 2006 were identified. Patients' ages ranged from 22-82 years (mean 48 ±12.3years.) About 54% of the patients were younger than fifty, while the peak frequency (28%) was in the 40-49 years age range (Fig 1).

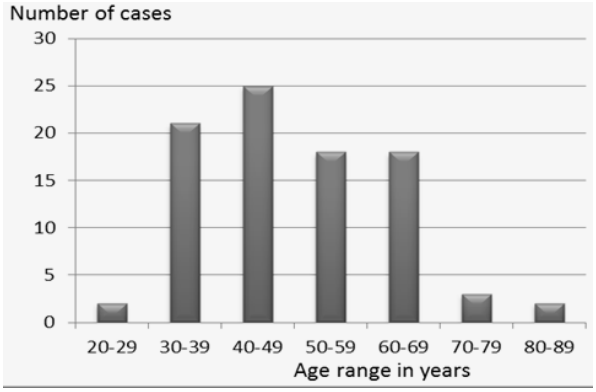

Figure 1: Age distribution of patients

Table 1: Histological types of Breast cancer

Histological type	No. of cases (%)
Infiltrating Ductal Carcinoma NST	73 (82)
Lobular Carcinoma	6 (6.7)
Mucinous Carcinoma	3 (3.4)
Papillary Carcinoma	2 (2.3)
Medullary Carcinoma	2 (2.3)
Ductal Carcinoma In-situ	2 (2.3)
Apocrine Carcinoma	1 (1.1)
Total	89 (100)

Table 1 shows histological types of breast cancer. Infiltrating ductal carcinoma of no special type (NOS) was the commonest histological variant with 73 cases (82%). Majority of the cases (69.7%) were grade 3 (Fig 2), 25.8% were grade 2 and 4.5% were grade 1.

Seventy-three cases were evaluated for ER and Her2/neu, and 67 for PR. Using the Allred scoring system[6] , 45 (61.6%) cases were negative for ER and 53 (79%) were negative for PR (Table 2).

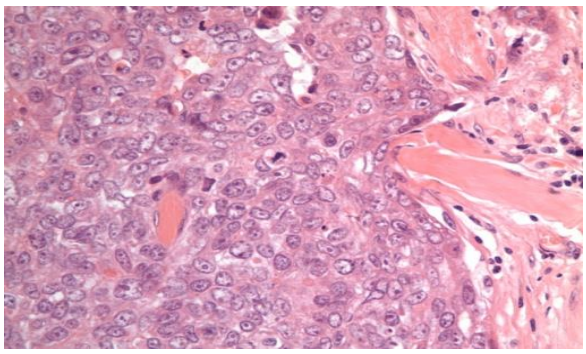

Figure 2: Photomicrograph showing Nottingham Grade III tumour. (H&E x40). The nuclei are highly pleomorphic, there is no tubule formation and mitotic count is high.

Table 2: ER and PR scores of all the cases

Allred score	ER Number of cases (%)	PR Number of cases (%)
0	45(61.6%)	53(71.9%)
2	1(1.4%)	2(3.0%)
3	3(4.1%)	3(4.5%)
4	3(4.1%)	1(1.5%)
5	3(4.1%)	1(1.5%)
6	3(4.1%)	2(3.0%)
7	8(11.1%)	2(3.0%)
8	7(9.6%)	3(4.5%)
Total	73(100%)	67(100%)

Table 3: Classification of cases based on the immunohistochemical profile

IHC groups	No. of Cases	%	Follow up Details
ER or PR Positive	24	41.4	5 Cases (20%) were dead within 2 years, 2 cases (10%) presented with recurrence. 17 cases (70%) lost to follow up
HER 2/ Neu Positive	3	5.2	All the 3 died within 1-2 years of presentation
Triple Negative	31	53.4	6 cases (20%) were dead within 3-5 years, 16 cases (50%) were alive and 9 cases (30%) lost to follow up

Three cases (4.1%) showed overexpression of Her2/neu. All the Her2/neu positive cases were ER/PR negative. Complete hormone receptor profile and Her2/neu IHC

results were not obtained for all the cases because of technical problems with antigen retrieval.

The 2 cases with equivocal Her2/neu score were later downgraded to negative after ISH test. Out of 58 cases with complete immunohistochemistry data, 31 cases (53.4%) were triple negative while 24 cases (41.4%) showed positivity for either ER or PR (Table 3).

Figure 3 shows a positive nuclear staining for ER. The clinical correlate of the 58 cases with complete immunohistochemistry data shows that 5 patients (9.1%) were first seen with TNM stage I disease,13 patients (22.7%) at stage II, 32 patients (54.6%) with stage III, while 8 patients(13.6%) patients presented with stage IV disease.

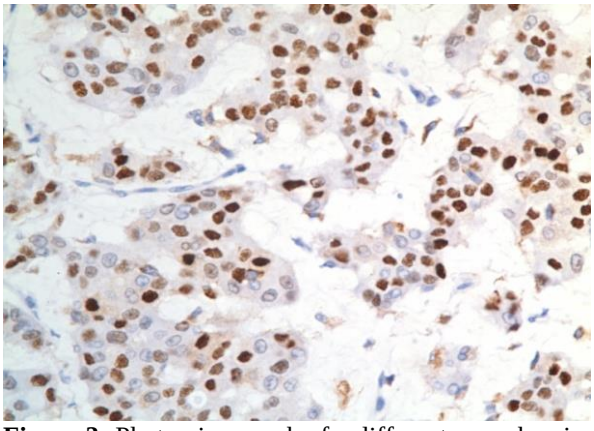

Figure 3: Photomicrograph of a different case showing positive nuclear stain for ER. X 10obj

Patients in our centre benefitted from surgery, adjuvant hormonal therapy, chemotherapy and radiotherapy. A combination of cyclophosphamide, Doxorubicin and 5-fluorouracil (CAF) was commonly employed for treatment of our patients.

After 5 years of follow up, out of the 24 ER/PR positive patients, 5 cases (20%) were dead, 2 cases 10% had presented again with local disease recurrence, while 17 cases (70%) were lost to follow-up. Out of the 31 patients with triple negative breast cancer, 16 (50%) were alive and well with no evidence of recurrence, 6 cases (20%) were dead and 9 cases (30%) were lost to follow-up (Table 3). All the 3 patients with tumours showing overexpression of Her2 had died within 1-2 years of initial presentation.

Discussion

This study shows a predominance of infiltrating ductal carcinoma (NOS) variant of breast cancer in our centre. This is in keeping with earlier studies in Nigeria which have documented the predominance of infiltrating ductal carcinoma (NOS) histologically and have equally shown that the disease occurs at a younger age, about a decade earlier than seen in Western countries (eg. UK and USA)[7,8]. In this study, the peak incidence was in the fifth decade, a decade earlier than seen in the developed countries[9,10]. There was also high incidence of breast cancer in the third and fourth decades of life. This is in contrast with the low incidence of breast carcinomas seen in British and Finnish women in these age groups[10]. Both observations may be explained by low life expectancy in Nigeria and the fact that women aged 15-49years constitute 53.6% of women in the study population[11]. Also there are younger women in the Nigerian population than previously described[12]. Genetic variations, reproductive factors which include history of induced abortion and miscarriages and increasing parity have been associated with breast cancer in the young[13].

The preponderance of infiltrating ductal carcinoma and the early age of occurrence in our study may be further supported by our finding of a large proportion of our patients being triple negative for ER, PR and Her2/neu. In other studies, genetic profiling has associated triple negative breast cancer with genetic mutation in BRCA1[14,15]. BRCA mutation was not examined in this study.

The histological grade of breast cancer in this study shows 69.7% of grade III carcinoma. This is comparable to the histological grade of breast cancer documented in different centres across Nigeria which also show a high preponderance of grade III cancers[16,17]. Studies have used histological grading independently and as a component of Nottingham Prognostic Index to predict biological behaviour of tumour and outcome of management of breast cancer cases[18,19]. In all these studies, grade III cancers generally, have shown poor prognosis. The preponderance of grade III cancers in our study may further support the findings of other studies in our centre which have shown breast cancer cases to be of poor prognosis; with patients presenting late with large tumour sizes, lymph node metastases and overall poor outcome of management with chemotherapy[3,20].

The significant proportion of our cases was ER/PR negative. Previous studies have documented high receptor negativity among breast cancer cases in Nigeria[8,17]. In a study by Savage et al breast cancer cases in blacks have lower expression of ER than in whites[21]. However in contrast to our study and other studies mentioned earlier, Adebamowo *et al* in a prospective study found a high percentage of hormone receptor positive breast cancer cases in a Nigerian cohort[22]. The discrepancies in the results obtained from these studies may be attributed to the fact that the cases enrolled for the studies presented at different health facilities in the country at different times with different methods of sample collection and processing and variable IHC techniques. Her2/neu over expression in our study is very low and in agreement with the findings of Adebamowo *et al*[22].

A clinical correlate of the triple negative breast cancer cases seen in this study shows an unusual pattern. After 5 years of follow-up, 50% of the patients, most of whom presented with stages I and II diseases and having triple negative IHC results were alive and well without

any evidence of local or distant tumour recurrence. This is at variance with previous studies on triple negative tumours which report a significantly more aggressive behaviour than other molecular subgroups[23,24,25]. In a study by Haffty *et al*, poor clinical outcome was seen in triple negative breast cancer cases even when they presented with early stage disease[26]. A recent study by Carey et al however documented chemosensitivity to anthracycline plus taxane neoadjuvant chemotherapy in triple negative breast cancer[27]. It is important to note that the patients in our study did not benefit from other chemotherapeutic option apart from cyclophosphamide, adriamycin, 5-fluorouracil (CAF). The unusual survival seen among the triple negative breast cancer cases that were given the same therapeutic option with all other breast cancer cases might have been that the triple negative breast cancer cases benefited more from the general chemotherapeutic treatment. Our finding is also in agreement with a previous conclusion drawn by Adesunkanmi *et al* which documented an unpredictable behaviour shown by breast cancer cases, also seen in our centre, in relation to established histopathological and clinical prognostic factors[3].

Conclusion

In conclusion though our data may be small, it suggest that breast cancer in Nigerian women occurs at a younger age, is commonly of a high histological grade and is more likely to be triple negative. Our clinical follow up data show that the instituted general chemotherapy for all cases may have been more beneficial to the IHC triple negative group and may not have been helpful to the IHC group with Her2/neu over-expression. However the large number of cases lost to follow up, especially as recorded in the ER/PR positive group would suggest the need for a better structured study.

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