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SERIES OF RARE CASES OF BREAST TUMOUR: 8-YEAR REVIEW AT MANKWENG BREAST ONCOLOGY CLINIC, LIMPOPO, SOUTH AFRICA

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Abstract

Breast cancer remains the most common cancer in many parts of the world, particularly for women. In March 2015, a Breast Oncology clinic for breast cancer patients was established at Mankweng Hospital. Invasive ductal carcinoma is the most common (87 %) tumour found in Limpopo, and occasionally, another rare tumour of the breast is presented in the Breast Oncology clinic.

The aim: The main objective is to share the experience of a rare tumour of the breast came across over the past 8 years since the establishment of the Breast Oncology clinic.

Material and Method: Series of rare case reports of Breast tumours and literature review from the Mankweng Breast Oncology Clinic.

Result: Rare tumour encountered in Breast Oncology clinic: adenomyoepithelioma, micro-papillary carcinoma of the breast, primary malignant melanoma of the breast, primary non-Hodgkin's lymphoma of the bilateral breast, advanced breast cancer in a case of Down's syndrome, primary neuroendocrine invasive breast carcinoma, sarcoma of the breast.

Conclusions: Most of these rare cases are presented to the Breast Oncology clinic in the advanced stage. Breast cancer awareness campaign is highly important for women in Limpopo, particularly when attending primary health care for any other conditions.

Keywords: breast cancer, Mankweng breast oncology clinic, rare.

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1. Introduction

Breast cancer remains the most common cancer in many parts of the world, particularly for women [1]. According to Globocan 2021, breast cancer has become the most common cancer diagnosed in all gender, surpassing that of lung cancer [2]. Among the female population, breast cancer is the most common malignancy in many countries (154 out of 185 countries), except in West Africa, where cervical cancer prevails [3]. The incidence estimates increased from 2.1 to 2.3 million new cases over the period from 2018 to 2020 [2].

In addition, breast cancer also represents the highest cancer mortality rates in women across the globe (103 out of 185 countries) [3]. Invasive ductal carcinoma no special type (IDC-NST) is the most common histological subtype, constituting about 40 % to 75 % of all invasive breast carcinomas [4] & Invasive lobular carcinoma is the second largest biologically distinct carcinoma, representing about 5 % to 15 % of all newly diagnosed cases and generally affecting women of advanced age [5]. Kohler et al. reported that IDC was the most common (86 %) histological type in Malawi [6]. Another study in southwestern Nigeria found 88.9 % invasive ductal carcinoma of no special type from the 10-year retrospective study [7]. A similar trend was found among the women in Limpopo [8].

In March 2015, a Breast Oncology clinic (BOC) was established at Mankweng Hospital to take care for breast cancer patients. This hospital is a tertiary teaching institution of the University of Limpopo, located 30 km east of Polokwane, the provincial capital. BOC at Mankweng Hospital was one of the facilities in the public sector in Limpopo, serving a population of 5.98 million people [9]. Most (87 %) of our patients were Invasive ductal carcinoma [8]. However, occasionally we get another rare tumour of the breast in the Breast Oncology clinic.

The main objective is to share the experience of a rare breast tumour that has come across over the past 8 years since the establishment of the Breast Oncology clinic.

2. Materials and methods

Description of Clinical cases of rare breast tumour patients who presented in Mankweng Academic Hospital for 8 years from 2015 to 2023 and literature review.

3. Result

3. 1. Adenomyoepithelioma

Adenomyoepitheliomas of the breast are rare benign breast neoplasms. They are characterized by proliferations of both epithelial and myoepithelial cells. Epithelial cells resemble those normally covering the mammary ducts. Myoepithelial cells include specialized epithelial cells with a myoid differentiation. They contain normal components of the lobular units of the breast tissue lying between the epithelial layer and basement membrane of ducts along with acini [10].

Although adenomyoepitheliomas are benign neoplasms, they have, however, a potential for recurrences and malignant transformations. The malignant adenomyoepithelioma is difficult to differentiate from other benign diseases such as intraductal papillomas, tubular adenomas, or sclerosing adenosis [11].

Case presentation

The 69-year-old, post-menopausal woman presented to the hospital with 18 months history of the left breast mass. She reported being previously treated with local excision of the breast mass 16 months ago at her community hospital when the mass was smaller, but a few months later, the painful mass recurred, growing rapidly. The patient had repeat resection of the recurrent tumour at the same local hospital 7 months before admission to our institution as the tumour continued to grow. There was no family history of breast cancer. The physical examination revealed breast asymmetry, a mobile, irregular breast mass measuring 14 cm × 9 cm in the retro areolar and left inner quadrant region with an old 3 cm scar (**Fig. 1**).

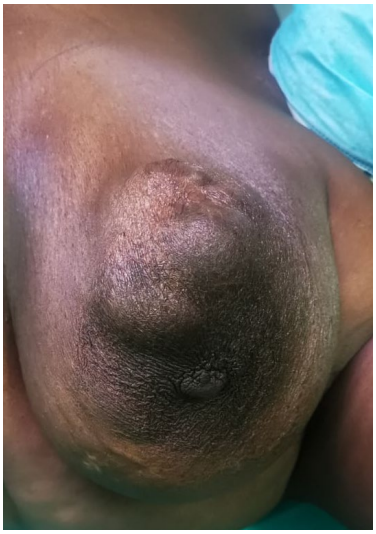


Fig. 1. Location of the mass in the retro-areolar area

The axillary lymph nodes were not palpable. Mammogram reported: left breast high-density irregular mass with indistinct margin posteriorly. Mass size: 12.9 cm × 5.7 cm on a craniocaudal view, extending from the retro-areolar region and the left inner quadrant. The tumour was associated with scattered fine microcalcifications. There was no focal or diffuse skin thickening. The conclusion of the mammogram report was breast imaging-reporting and data system (BIRADS)-5 breast tumour. The histology of an excisional biopsy revealed morphological features of adeno-

myoepithelioma, with the neoplasm noted to extend to resection margins. Immunohistochemistry described: P63 and CD 10 highlight the myoepithelial cell component, and CK7 highlights the luminal epithelial cells. A simple mastectomy with a sentinel lymph node biopsy was done successfully without complications. Histological features of mastectomy specimens were keeping with adenomyoepithelioma showing all resection margins free of tumour and reactive follicular hyperplasia in axillary lymph nodes.

Discussion

Neoplasms of pure myoepithelial or mixed epithelial and myoepithelial origin have been described in the salivary glands but are rare in the breast [12]. The first case of breast adenomyoepithelioma was described by Hamperl in 1970 [11]. Most patients with adenomyoepithelioma are elderly [10, 12], although it has also been reported in young patients. The specified age range is from 22 to 92 years, with a mean onset age of approximately 60 years [11]. Tumours usually appear as solitary, nodular palpable masses. Mastalgia and nipple discharges are rarely reported [10, 11]. In this case, the patient was an elderly 69-year-old & presented with a nodular mass associated with pain. Adenomyoepitheliomas have been classified histologically as tubular, lobulated, or spindle-cell types of growth patterns [13]. The most common microscopic type is the tubular type. Spectrums of histological patterns depend on noticed relative amounts of proliferating glandular and myoepithelial cells [14]. In immunohistochemical investigations, adenomyoepitheliomas reveal the epithelial cells highlighted with antibodies to cytokeratins (CK). The myoepithelial component reacts with the antibodies to smooth muscle actin, smooth muscle myosin, calponin, p63, desmin, and S-100. [15, 16]. As presented in our case, luminal epithelial cells showed antibodies to CK7, and myoepithelial cells highlighted P63 and CD10.

The radiological features of breast adenomyoepithelioma are not well described. Predominant ultrasound and mammogram findings demonstrate an irregular mass with suspicious imaging findings [10, 15]. In our case, investigations showed an irregular mass and fine microcalcifications, BIRADS-5 highly suggestive of malignancy.

Like others described in the literature cases, recurrences may be associated with incomplete resections of the original tumour. Reported recurrences appear as soon as 4 months and as late as 23 years after primary tumour excisions [15]. Our patient had the recurrence twice within 18 months of presentation. The recommended surgical treatment of adenomyoepithelioma involves wide local excisions with confirmed negative resection margins. Simple mastectomies or extended resections are advocated for cases with incomplete margin excisions [11]. We offered our patient a simple mastectomy with a sentinel lymph node biopsy. Surgical margins were free of tumour cells with no malignant deposits to axillary lymph nodes. The patient will continue follow-ups in the Mankweng Breast Oncology clinic to assess the outcomes.

Adenomyoepitheliomas of the breast have a risk of recurrences and are best treated with wide local excisions obtaining clear surgical margins. Close follow-ups are essential to assess recurrences and /or malignant transformations.

3. 2. Micro-papillary carcinoma of the breast

Invasive Micro-papillary carcinoma (IMPC) of the breast is a clinically aggressive rare form of invasive ductal carcinoma (IDC), accounting for less than 6 % of the cases of breast carcinoma [17]. There are no specific distinguishing features to differentiate between invasive micropapillary breast carcinoma from invasive ductal carcinoma, and 80 % of patients have lymph node metastasis at presentation with histological findings highly positive for ER (88 %) and c-erbB-2 (84 %) [18–20]. IMPC was first described in 1980. It has been thought that due to its higher propensity for lymph vascular invasion and lymph node metastasis, these patients experience worse outcomes than those with IDC [18–21]

Case presentation

An 81-year-old African female patient presented at Mankweng breast oncology clinic (Limpopo, South Africa) as a referral from a peripheral hospital. The main complaint was progressive

swelling of the left upper limb involving the ipsilateral breast. According to the patient, she had a prick on the left hand for more than 18 months; from then, her upper limb had been progressively swelling, which ultimately led to left breast involvement. She consulted various traditional healers at the time when she started experiencing symptoms; however, there was no improvement in her condition. It was at this point that she started seeking medical attention at her local hospital more than a year later after the onset of her symptoms. A biopsy on the breast mass was done on the initial presentation before the breast oncology referral.

She was a previously healthy individual, multiparous with a total of 5 children. The onset of menarche and menopause is not known, and no significant family history of breast cancer.

Upon examination, the left upper limb was swollen from the fingers to all the way through the shoulder joint and also involved the left breast. There were multiple ulcerated lesions and masses of various sizes on the breast, axilla and shoulder region shown in **Fig. 2**. There were notable peau D'Orange skin changes and nipple retraction. On the contralateral upper limb, there were no significant findings, and the examination of the system was unremarkable.

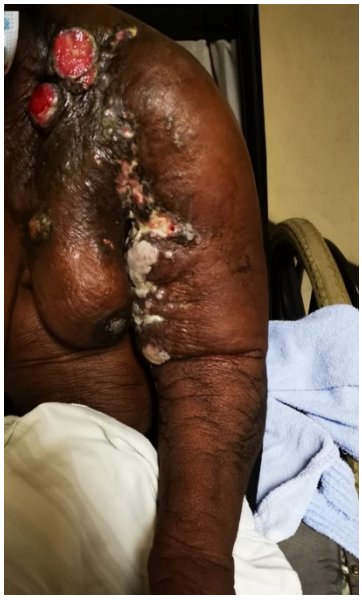


Fig. 2. Advanced left-sided breast cancer with ulcerated lesions, masses of various sizes, and also extending to the left upper limb

Histopathological evaluation of the incision biopsy, the left breast mass showed skin-surfaced tissue involved by invasive neoplasm. Small nests of malignant cells largely involve lymphatic vessels. Markedly pleomorphic cells, displaying brisk mitotic activity and showing no tubule-forming behaviour. These features are in keeping with invasive micro-papillary breast carcinoma. The patient was referred to medical oncology clinic; however, she ultimately succumbed to her illness before her treatment.

Discussion

The most common presentation of IMPC is a breast lump (61 %), which may be associated with nipple retraction and/or erythema. The left breast has been shown to be commonly involved accounting for 71 % of the IMPC cases, right breast (25 %) and bilateral breast (3 %) [17]. In our case, the patient has the IMPC on the left side. Imaging studies show features are those of a typical breast malignancy, with MRI further showing features of lymphatic image infiltration [17].

IMPC is presumed to be more aggressive than IDC; furthermore, patients with IMPC present with higher clinical stages and higher histological degrees, as well as higher rates of lymph vascular invasion and axillary lymph node extracapsular extension [20, 21]. IMPC patients have been shown to have an unfavourable prognosis for loco-regional recurrence than IDC patients.

However, overall survival, relapse-free survival (RFS) (OR; 2.04; 95 % CI: 1.63–2.55) and local, regional recurrent-free survival (LRRFS) (OR: 2.82; 95 % CI: 1.90–4.17) compared with IDC showed that statistically there is no proven significant difference in mortality between IDC and IMPC [20–25] indicating that radical or proactive clinical therapy is unnecessary. Treatment remains individualized to include tailored therapeutic interventions/multidisciplinary approaches.

Invasive micro-papillary carcinoma is a rare, aggressive variant of breast cancer. Its frequent lymph-vascular invasion and high tumour grades correlate with its aggressive nature. However, no significant difference in overall survival has been yet proven. Patients must be encouraged to seek medical attention early as this can aid in a better prognosis and reduce mortality and morbidity.

3. 3. Primary malignant melanoma of the breast

Melanomatous lesions of the breast may occur as a metastatic manifestation of primary cutaneous melanoma or as true primary malignant melanoma of the breast (PMMB) [26, 27]. Metastasis from cutaneous malignant melanoma represents the majority of cases of melanoma involving the breast [28]. PMMB, however, is a rare entity and accounts for 3–5 % of all melanomas and for <0.5 % of malignant breast tumours [26, 29].

The South African breast cancer policy developed as a series of standards of care, but not for PMMB. The aim of this process is to ensure that high-quality and appropriate care administers in the diagnosis and management of patients, irrespective of their geographical location or social circumstances. Early detection followed by appropriate treatment is currently the most effective strategy to reduce breast cancer mortality.

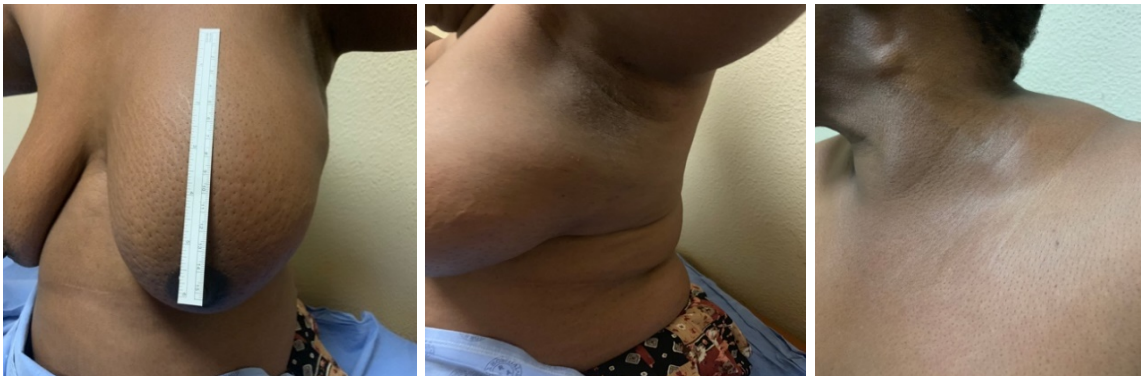
National cancer registry statistics in South Africa show that malignant melanoma diagnosed histologically in females and males, with all population groups combined, is at 2.00 and 2.36 per cent, respectively [30]. Therefore, extrapolation from this data yields results that suggest that non-cutaneous breast malignant melanoma remains an unrecognized and indeed rare variant of malignant melanoma. Only a few cases of PMMB derived from the breast parenchyma without skin involvement have been reported in the literature and whereas less than 190 cases have been reported from the skin overlying the breast [31].

Case presentation

An elderly African female patient known as hypertensive with vitiligo was referred to the breast oncology clinic, Makweng hospital (South Africa), with a six-month history of painless left breast swelling with a fast-growing mass associated with axillary and neck swelling on the ipsilateral side and no nipple discharge. There is no notable personal or family history of previous diagnoses of malignancies. She admits to having used alternative medicine and, at one stage, consulted with traditional healers.

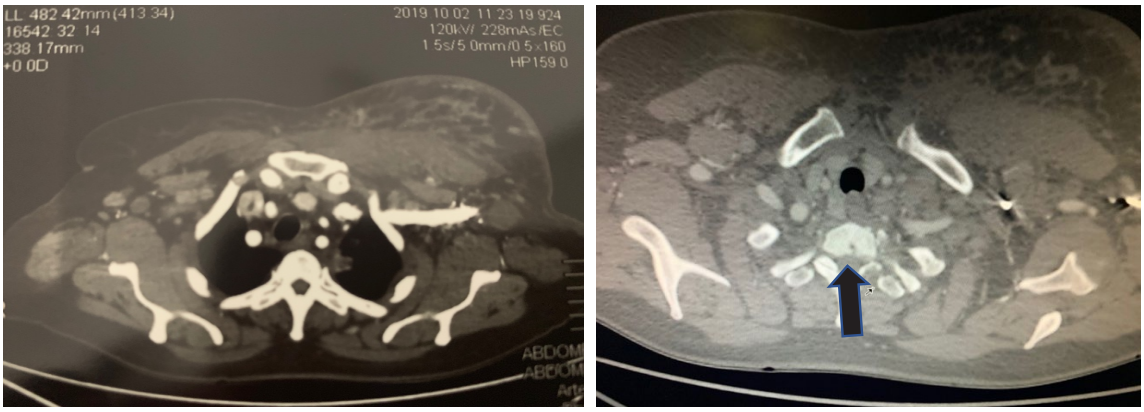
Local clinical examination revealed breast asymmetry, left breast peau d'orange, 15 cm by 15 cm palpable irregular mass in greatest dimension with no chest wall involvement. There was a matted lymph node in the Left axilla and supraclavicular region; refer to **Fig. 3, *a–c***. No cutaneous, mucosal or ocular lesion was detected, and all other systems on physical examination were unremarkable. Mammographic findings revealed BIRADS 4B, with moderate suspicion for malignancy and multiple left axillary lymph nodes with reduced fatty hilum. Imaging with a computed tomography from the base of the skull (BOS) to the pelvis revealed an apparent left breast invasion with a malignant mass and extensive lymphadenopathy with metastatic deposits on the thoracic vertebral body, as depicted in **Fig. 4, *a, b***.

Histopathological evaluation of the left breast core biopsy revealed cells with a moderate amount of eosinophilic cytoplasm and melanin pigment. The nuclei were markedly pleomorphic with vesicular chromatin. Mitotic activity was noted, inclusive of atypical cells. Immunohistochemical stains performed revealed S100 focal positivity, Leucocyte Common Antigen (LCA) negative within the tumour cell, Melanin A positive, and Microphthalmia-Associated Transcription Factor (MITF) positive. The conclusion suggested features consistent with malignant melanoma.



a *b* *c*

Fig. 3. Breast asymmetry: *a* – left breast mass, 15 cm by 15 cm; *b* – Enlarged left axilla lymph node; *c* – enlarged supraclavicular lymph node



a *b*

Fig. 4. Computed tomography: *a* – left breast invasion with a malignant mass and extensive lymphadenopathy; *b* – with metastatic deposits on the thoracic vertebral body

Discussion

Malignant melanoma of the breast has four predominant manifestations: i) primary malignant melanoma of the breast skin; ii) malignant melanoma metastasis to the breast; iii) in-transit metastases to breast tissue and skin; and iv) primary malignant melanoma of the breast gland [26]. Cutaneous and non-cutaneous melanomas differ in their epidemiology even though they have a shared cell of origin. Non-cutaneous melanomas tend to present at an older age and to be diagnosed at a more advanced stage [32].

Breast cancer mortality rates remain high in low & middle-income countries due to late presentation and inadequate access to optimal care [33]. In spite of the rapidly growing mass, our patient came to the clinic 6 months after discovering the first signs. As a result, she had already metastasis to the supraclavicular region and bones.

Prognosis is usually poor at the time of diagnosis [34, 35]. However, management is considered to be important and significantly affects prognosis. The treatment involves critical primary surgical resection with an appropriate combination of chemotherapy, radiotherapy, immunotherapy and targeted therapy [26, 32, 36]. Radical surgical resection with free margins combined with axillary node resection or axillary sentinel node resection is the primary treatment of choice [28]. Chemotherapy is commonly used for pre-and postoperative adjuvant therapy and for those who are not suitable or refuse surgery, or for those patients who exhibit widespread metastases, such as our patients who had metastasis to the bone. The chemotherapy programme is usually based on a dacarbazine-based treatment plan; however, the effective rate is only 7–13 % [37]. Other commonly used agents include temozolomide, cisplatin and taxol; multi-agent chemotherapy may improve the treatment outcome.

Melanomas at these unusual sites generally carry a worse prognosis [35]. Early diagnosis is presently the key to proper treatment and improved survival for patients with these unusual variants. Awareness of early signs and symptoms of breast cancer is important in order to facilitate early diagnosis before the disease becomes advanced, consequently enabling more effective or simpler therapiesMalignant melanoma predominantly affects the skin and mucous membrane; hence our experience with its extra-cutaneous primary breast melanoma invoked our interest to address and emphasize timeous breast cancer screening and treatment. The diagnosis still follows a thorough, appropriate triple assessment.

3. 4. Primary non-Hodgkin's lymphoma of the bilateral breast

Non-Hodgkin's lymphoma (NHL) is a common AIDS-defining malignancy; however, it remains a rare extranodal malignant tumour of the breast, and its prevalence is poorly not univocally described [38]. Primary breast lymphoma (PBL) is an uncommon disease occurring in 0.4–0.5 % of all breast malignancies. Diffuse large B-cell lymphoma (DLBCL) is the most common histological diagnosis [39]. Bilateral breast lymphoma is a very rare tumour during the pregnancy and postpartum period, but highly invasive and associated with a poor prognosis if left untreated. Early diagnosis is crucial for outcome [40]. This case, presented to us, is the first bilateral breast lymphoma we found in our Breast Oncology Clinic in Mankweng Hospital.

Case presentation

Eight-month postpartum, thirty-year-old female patient who was HIV positive with an absolute CD4 count of 824 cells/uL on antiretroviral medication presented to the General Outpatient Department with a history of bilateral breast swelling, pain and skin discolouration associated with night sweats and fever for a period of one month. Physical examinations during the first visit to the Breast Oncology Clinic revealed remarkably enlarged breasts, as shown in **Fig. 5–7**, and palpable enlarged lymph nodes in both axillae.

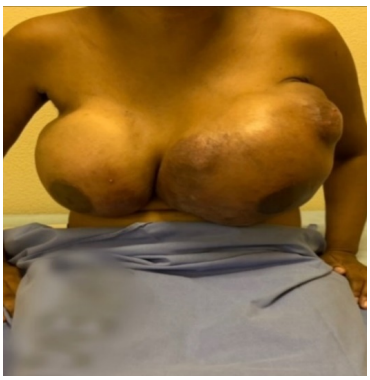


Fig. 5. Breast lump and size (Bilateral)

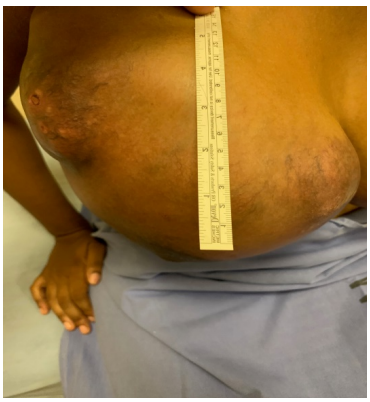


Fig. 6. Right breast mass

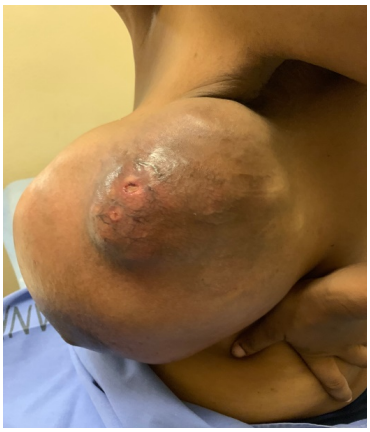


Fig. 7. Left breast mass

All other systems on a physical examination were normal. Investigations: ultrasonography showed bilateral breast dense masses, left and right axillary lymphadenopathy: BIRADS 3. Abdominal ultrasonography was grossly normal. The report of core biopsy reflected: «Histology and immunohistochemistry observed malignant cellular infiltrate with cells that have a diffuse sheet-like pattern of growth and mitotic activity noted a high-grade non-Hodgkin B-cell lymphoma compatible with a diffuse large B-cell lymphoma, germinal centre subtype». The bone marrow aspiration was done, and no abnormality in the specimen was noticed. The patient was booked to the Medical Oncology Clinic for consultation and treatment. Regrettably, within a one-month period patient's condition deteriorated with difficulties of breathing and bleeding from ulcerative lesions of the breast masses. The patient was admitted urgently to the hospital and died soon before commencing chemotherapy.

Discussion

Of people living with HIV, 25–40 % will develop a malignancy, with about 10 % having non-Hodgkin's lymphoma [41]. NHL are malignancies that originated in lymphoid tissue, but the aetiology of NHL is poorly understood today; however, the most significant risk factor for the development of all NHL is the immunodeficiency state [42].

B cell lymphomas can arise at any stage of normal B cell development; however, most of them are derived from cells that have been exposed to the reaction of germinal centres. DLBCL is an AIDS-defining malignancy and the most common histologic subtype of non-Hodgkin lymphoma [39, 43].

HIV infection results in impaired cellular immunity, which predisposes to the development of cancers [41]. As the lifespan of HIV-infected patients has lengthened, malignancies increasingly contribute to morbidity and mortality in this population [44]. Since the routine implementation of antiretroviral therapy, cancer has been diagnosed in more than 40 % of HIV-infected patients, and more than 28 % of HIV-related deaths are attributable to malignancy [45]. AIDS-related NHL can be divided into three general categories based on location: systemic NHL, primary central nervous system lymphoma and primary effusion (or body cavity) lymphoma [46]. Systemic NHL accounts for the great majority of AIDS-related lymphomas. Systemic NHL can be further divided into common subtypes described in the World Health Organization classification system. The most common systemic NHL subtypes seen in HIV-positive persons are Burkitt lymphomas, approximately 25 %, and DLBCL, approximately 75 % [46, 47].

Bone marrow (BM) is the most common site of extranodal involvement of lymphoid malignancies, and the frequency of BM involvement varies from 20–100 % according to the lymphoma subtype [48]. There are also situations where BM is the only accessible site to make the diagnosis of NHL. Bone marrow involvement with NHL is usually focal, but on rare occasions, patients may have extensive NHL confined to the bone marrow, presenting clinically with pancytopenia and systemic symptoms [49].

The prognosis of PBL is fair but poor in pregnant or postpartum women with bilateral breast lumps [40, 50]. Cytotoxic chemotherapy remains the primary means by which these lesions are treated. Radiation therapy can also be used in an adjuvant setting. Many patients can avoid mastectomy if systemic chemotherapy is used as the initial form of treatment. Survival in patients treated with cytotoxic chemotherapy has improved over the last several years [43].

DLBCL is curable in approximately half of the cases with current therapy, particularly in those who achieve complete remission with a first-line treatment. Factors that contribute to outcome include age, socioeconomic conditions, comorbid conditions, performance status, and various clinical features [51]. The International Prognostic Index and its variants are the main prognostic tools used in patients with DLBCL. These indices are significantly more accurate than standard staging criteria in predicting long-term survival [52].

Confirmation of diagnosis in patients with bilateral breast lymphoma in pregnant or postpartum patients is frequently delayed because of breasts' extraordinary engorgement, hormonal changes during the pregnancy or lactation. Most of those patients also are diagnosed usually in advanced stages [50]. The case presented to us; the condition was worsening rapidly within a month from the first arrival at Breast Oncology Clinic. The patient died soon after admission to the hospital. It is important that any pregnant or lactating woman with an abnormal bilateral breast enlargement should undergo speedy diagnostic investigations, and in the case of NHL, the treatment should be implemented as soon as possible.

Primary non-Hodgkin's lymphoma of bilateral breasts is uncommon. It grows rapidly during the antenatal and postpartum periods, especially in the HIV population. Urgent attention is required for prompt investigations of breast lumps in pregnant or postpartum HIV patients, which must be followed with immediate treatment if proven NHL.

3. 5. Advanced breast cancer in a case of Down syndrome

Down syndrome is a genetic condition characterized by the presence of all or part of an extra chromosome 21 and is linked to a spectrum of medical and phenotypic features [53–55]. Chromosome 21 is associated with tumour suppressor gene expression, and hence the presence of this extra chromosome in the genetic alteration allows for some favourable effects making it one of the most powerful natural protection agents against many solid tumours such as breast cancer in women [55]. On the other hand, individuals with trisomy 21 tend to have societal and hormonal risk factors for breast cancer, including frequent nulliparity, lack of breastfeeding, physical inactivity and high body mass index [56]. Unfortunately, so they are also prone to blood cancers such as leukaemia [57].

Over the years, with advances in medicine, the life expectancy of individuals living with Down syndrome has increased markedly from 25 to 60 in the past 30 years [58]. With that came questions as to whether screening policies should also apply to the Down's syndrome population as compared with the general population; in particular, screening policies such as mammography have been looked at, and it was found that it did not serve much of a clinical benefit and it was in fact found to be financially costly, with the cost per finding being high, the benefit of mammograms is hence questionable, and the potential for harm appeared greater as from previous and current studies have demonstrated that less than 1 % of the women with downs syndrome develop breast cancer [58–61].

This case report was inspired by the first reported case of triple-negative breast cancer by N. Dey [54]. It was the first of its kind to be reported in the literature, and in this case, we report a similar case of breast cancer in Downs syndrome subtype luminal B, stage 4 breast cancer in a 26-year-old young lady hoping to bring further insight into this rare condition and hopefully adding further into research that will assist in gaining more insight into this condition.

Case presentation

A 26-year-old female patient presented at Limpopo, Mankweng breast oncology clinic as a referral from the peripheral hospital. She was born in a rural township, being one of 6 siblings at a young age; her mother had always noticed that her development was grossly delayed compared to the other children. She was born with Down syndrome and, early on from birth, was noted

to have hypothyroidism, and no other associated congenital defects were detected. She was solely cared for by her family and was never able to go to school due to the need for special schooling and the family's financial constraints.

This young lady and her mom started noticing a lump in her left breast which had been progressively growing over the past 2 years. It was not painful; no associated skin changes or nipple discharge, and no axillary masses were noted. Menarche was reported to have been at 15 years of age, experienced regular menstrual periods, was not on contraception and has never been reported to be pregnant.

Though she was noted to have low thyroid levels at birth, she was not on treatment and was clinically euthyroid. She had no previous operations and no comorbid conditions of note. The patient had just completed neo-adjuvant therapy within a week of presenting. Prior to chemotherapy, she was assessed as having stage 4 breast cancer, tumour size 7 cm in its greatest diameter in the left upper outer breast quadrant, no skin or chest was involved, and there was ipsilateral axillary lymph node involvement and metastasis to the thoracolumbar spine detected on bone scan. Family history, as well as social history, was non-contributory. Upon examination: She was of short stature and had physical features in keeping with Down's syndrome. Vitals were stable with the following readings: Blood Pressure 100/67 mmHg, pulse 75, apyrexial and weight of 65.5 kg. Breast examination showed asymmetrical breasts, with the left one showing a bulge over the upper outer quadrant. No skin changes and no palpable axillary lymph nodes. Palpable mass on the outer upper quadrant, 5 cm in its widest diameter, not attached to the skin of the chest wall, clinically stage 4 with bone metastasis to 9^{th} thoracic vertebrae and 5^{th} lumbar vertebrae, with the rest of the systematic examination being unremarkable. Histology results from a core biopsy confirmed an infiltrating ductal subtype\carcinoma of no special type. Modified and bloom and Richardson grading score: tubules 3, pleomorphism 3, mitoses 1, and total score of 7, making it a grade 2\moderately differentiated adenocarcinoma. Immunohistochemistry: oestrogen receptor-positive, progesterone receptor positive, HER2 positive, and Ki-67 of 8 %, making it a luminal B molecular subtype. Mammogram findings: BI-RADS 5, highly suggestive of malignancy on the left breast. Bone scan: bone metastasis localized to thoracic vertebrae 9 and lumbar vertebrae 5. Tumour marker CA 15-3 was 7. The patient had a good clinical response to chemotherapy, and a simple mastectomy was done.

Discussion

To the best of our knowledge, from the currently existing literature, this case is similar to the previously described case of triple negative breast cancer in Downs syndrome [54]. But it is the first of its kind to ever be described as it is an advanced stage 4 luminal B (HER2+) breast cancer in an African female. Among the many genes expressed in chromosome 21, one particular importance is RUNX1. Runt-related transcription factor 1 (RUNX1), also known as acute myeloid leukaemia 1 protein (AML1) or core-binding factor subunit alpha-2 (CBFA2), is a protein that in humans is encoded by the RUNX1 gene [62]. RUNX1 plays a critical role in the early stages of haematopoiesis and is often expressed in breast epithelium and is deregulated during tumorigenesis. It has been noted that RUNX1 functions as both an oncogene and tumour suppressor gene in breast cancer, acting as a tumour suppressor in oestrogen receptor-positive tumours and an oncogene in oestrogen receptor-negative tumours [62]. Understanding the role of RUNX1 does provide some insight into why individuals with Down syndrome have a higher risk of leukaemias and a reduced case frequency of breast cancer. More studies are needed to further clarify this, and hopefully, in future, we will be able to propose screening techniques for individuals living with Down's syndrome who may have an increased risk of also developing breast cancer rather than using the same screening techniques used for screening non-Down's syndrome patients, which from several pieces of research has been shown to be of no clinical benefit and costly [60].

The patient in the case study has breast cancer which has been classified with the use of immunohistochemistry as luminal B (oestrogen receptor-positive, progesterone receptor-positive, HER2+ and Ki 67 of 8 %) molecular subtype. Based on a study conducted at Third Hospital of Nanchang City over a period of 2005 to 2015, luminal B was found to be the commonest subtype, with the majority of the individuals being below the age of 50 (p-value; 0.018) [63]. Furthermore, luminal B

has been associated with unfavourable clinical outcomes such as Clinical features [64–66]. Poorer disease-free survival, increased risk of early relapse, appears to be limited to the early period after surgery and within the first 5 years after diagnosis, predisposition to relapse in bone and pleura, similar to luminal A, with bone metastasis more common than lung, relative insensitivity to endocrine therapy compared with luminal-A subtype and relative insensitivity to chemotherapy compared with basal-like and HER2-positive subtypes. With such poor clinical outcomes, the need for early detection, diagnosis and having individualized treatment strategies remains an area of crucial importance, more so for individuals living with downs syndrome as other than intellectual disability, social and financial constraints, they suffer from other medical conditions that can alter adherence to treatment and follow up as luminal-B has been shown to have a poor response to hormonal and chemotherapy [65]. Management stills remains a challenge for individuals with luminal-B breast cancer.

The luminal-B subtype remains a clinically important classification of breast cancer with prognostic and potential predictive implications. Due to the nature of the impairments in individuals with Down syndrome, such as intellectual disability, it may be difficult for early recognition of many conditions, breast cancer included and hence posed an early detection and diagnostic challenge. For these reasons, an understanding of the relationship between breast cancer, molecular subtypes, and Down syndrome is vital for researchers, clinicians and the education of individuals living with Down syndrome and their families, more so for the formulation of individualized treatment strategies. For these reasons and more, more research is encouraged to further guide our understanding and hence aid in the formulation of management protocols relevant to this population.

3. 6. Primary neuroendocrine invasive breast carcinoma

Primary neuroendocrine carcinoma of the breast is currently considered a rare entity, and for this reason, there are no data from prospective clinical trials on its optimal management and is said to constitute approximately 0.3–0.5 % of all breast cancers [67, 68]. Neuroendocrine breast cancer, also known as breast carcinoma with neuroendocrine differentiation, is a group of heterogeneous rare tumours of invasive breast carcinomas [68] that have been historically poorly defined due to definitions of what constitutes a neuroendocrine carcinoma [69].

The are several proposed theories in literature with regard to the histogenesis of primary neuroendocrine breast cancer; the most recognized theory on the histogenesis of Neuroendocrine breast cancer (NEBC) suggests its derivation from the divergent differentiation of a neoplastic stem cell in both epithelial and neuroendocrine cells [69]. Another theory hypothesizes a derivation from neural crest cells that migrate to the mammary glands or an origin from neuroendocrine cells present in breast tissue [69]. The observation that NEBCs often resemble breast tumours in their histological features supports the hypothesis that NEBCs derive from the differentiation of an epithelial progenitor cell [69].

Furthermore, the term neuroendocrine carcinoma of the breast was revised to carcinomas with neuroendocrine features in the 2012 WHO Classification of tumours of the breast [67]. Diagnosis is based on morphological features similar to that of lung and gastrointestinal neuroendocrine tumours and neuroendocrine markers [68]. The World Health Organisation (WHO) has stratified neuroendocrine neoplasm based on their histological differentiation into low, intermediate and high grade, with the majority of the cases of NEBC being hormone receptor-positive and human epithelial growth factor receptor 2 (HER2) negative [70–72]. In 2019, the WHO classified neuroendocrine breast cancers with neuroendocrine tumours of other organ systems into differentiated neuroendocrine tumours (low Nottingham grade) and poorly-differentiated neuroendocrine carcinoma (NEC) (high Nottingham grade). This, therefore, excludes the previously named intermediate group, allowing only the recognition of two groups [73]. There could be further classifications and new findings in the future, which will hopefully shed more light on this histological type of tumour.

Neuroendocrine tumours commonly occur in the gastrointestinal system (70 %) and broncho pulmonary system (20 %), with mammary origin accounting for less than 1 % [71]. Early-stage tumours are usually treated with the same strategy used for the other types of invasive breast cancer [67, 68].

Case presentation

A 39-year-old female, obese patient presented at our clinic complaining of a right breast lump for 18 months duration. She initially attended her local hospital from the time when she noticed the right breast mass. A core biopsy was done and referred to the Mankweng breast oncology clinic for further assessment and management.

She was a previously healthy individual with no known comorbidities and no family history of malignancy. On enquiry of her gynaecology history, she stated that her menarche was at the age of 21, currently still having her normal periods and on contraception. She has a 15-year-old child, which she had at the age of 24. After the birth of her first child, she had 2 more pregnancies, all resulting in unexplained stillbirths at term. No history of pregnancy-induced hypertension or any medical conditions diagnosed during pregnancy. After the onset of the breast lump, she was at the time also diagnosed with young hypertension. No associated weight changes, retroviral disease negative. Upon examination, she had a scar on the right upper quadrant, no palpable axillary lymph nodes, and elevated blood pressure (150/93 mmHg, pulse 88), high body mass index (BMI) of 37.7 kg/M^2 and the rest of the vitals and systematic examination unremarkable. On local breast examination, she was clinically staged as T3N0M0 (Tumour-Node-Metastasis [TNM] classification), making it stage IIB.

Histological evaluation showed nests of cells infiltrating extensively throughout the tissue. Hormone receptor (ER & PR) positive and HER2 score 3+ and KI 67: proliferation index 50–60 %. Synaptophysin and chromogranin positive cytoplasmic staining are within the tumour cells, features in keeping with grade 3 invasive carcinoma showing neuroendocrine differentiation.

Mammogram (**Fig. 8**) revealed poorly marginated density with speculations noted on the upper inner quadrant at 1 o'clock on the middle portion of the right breast. Speculations are extending anteriorly to the retro-areolar space causing minimal traction of the peri-areolar skin and nipple. There is associated architectural distortions and trabecular thickening. The retro mammary space is grossly normal bilaterally. No thickening of the overlying skin and no dilated ducts bilaterally. Left breast regional benign calcifications. No visualized axillary lymph nodes bilaterally.

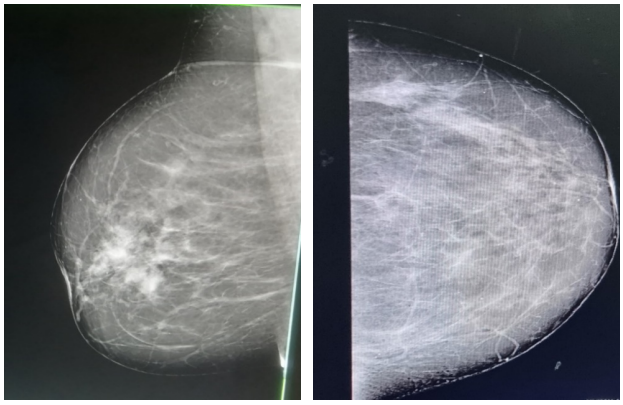


Fig. 8. Mammogram of the right breast (on the left) and left breast (on the right); poorly marginated density with speculations noted on the upper inner quadrant at 1 o'clock on the middle portion of the right breast

For further evaluation, a CT scan (**Fig. 9–11**) was done and reported multiple enlarged lymph nodes in the right axillary region. There is an ill-defined right breast with trabecular thickening and nipple retraction, and it does not extend into the retro mammary spaces; the pectoralis muscle is grossly normal. There are hypodense areas noted in the thoracic vertebrae with involvement of the posterior elements. The right scapular blade and spine also have multiple hypodense areas. Lung parenchyma is grossly normal, visualized liver is grossly normal, the stomach & rest of the visualized bowel are grossly normal, and kidney is grossly normal.

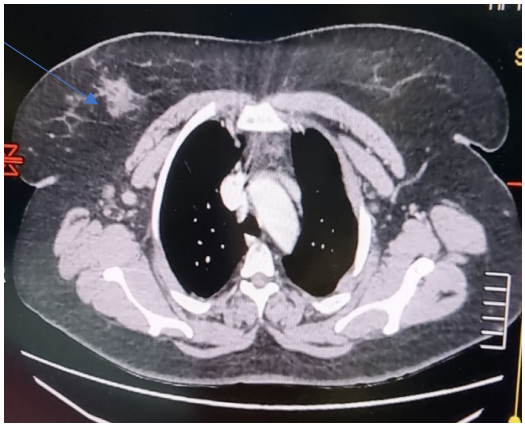


Fig. 9. CT scan; transverse view; there is an ill-defined right breast mass with trabecular thickening and nipple retraction, and it does not extend into the retro mammary spaces; the pectoralis muscle is grossly normal

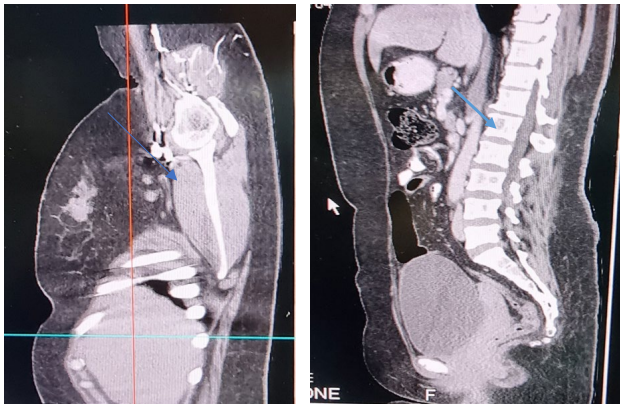


Fig. 10. CT scan; sagittal views; reported multiple enlarged lymph nodes noted in the right axillary region. There are hypodense areas noted in the thoracic vertebrae with involvement of the posterior elements. The right scapular blade and spine also have multiple hypodense areas

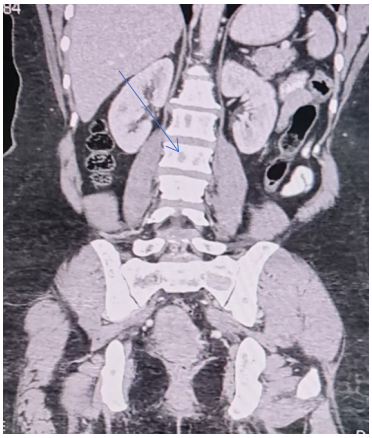


Fig. 11. CT scan chest abdomen coronal section; Hypodense areas noted in the Lumber vertebrae, visualized liver is grossly normal, stomach & rest of the visualized bowel are grossly normal, kidney are grossly normal

With the evidence at hand, the patient was evaluated as primary neuroendocrine breast carcinoma, newly diagnosed hypertensive on treatment with features suggestive of metastasis

to the bones. A bone scan was ordered and reported widespread metastasis to the skull, throughout the spine, pelvic bone, proximal femur and sternum. With this metastasis, the patient was re-assessed as clinically stage IV disease. The management approach changed to focus on palliative care. No surgical intervention was done; the patient was referred to the medical oncology clinic for further management and to come back if the need for surgical palliation arose.

Discussion

Primary NEBCs are rare, and hence a diagnosis depends on excluding metastasis from other sites because the two entities require different management approaches [74]. The use of diagnostic tools includes the use of tumour makers such as chromogranin (CGA) and synaptophysin (SYP) immune-reactivity, which is significantly associated with a neuroendocrine neoplasm [67] diagnosis compared with that to non-Neuro Endocrine Neoplasms (NENs) and displayed high sensitivity (CGA; 89 %, SYP; 100 %) and moderate to high specificity (CGA; 85 %, SYP; 58 %) [75]. It is important to know that elevated chromogranin levels are also associated with hypertension, obesity and heart failure [76], among other conditions.

Breast imaging for secondary NEBC is oval in shape with circumscribed or micro-lobulated margins on mammography and/or ultrasound [77]. Triple assessment is mandatory; however, histopathology assessment and immunohistochemistry staining are the mainstays of diagnosis [67, 78, 79]. Clinically, the presentation of NEBC cannot be differentiated from other types of breast cancer entities. It has also been postulated that, unlike other breast cancer entities, it can present with clinical features related to hormonal secretion because of ectopic production of adrenocorticotropic hormone, norepinephrine, or calcitonin [80].

Our patient is obese and hypertensive with Synaptophysin and chromogranin-positive cytoplasmic staining within the tumour cells. More knowledge and research on the possible association between tumour markers and clinical syndromes could play a vital role in the management of patients, and hence, further evidence on the association is of crucial importance.

So far, there is no available research data specifying the radiological pathognomic features in the diagnosis of NEBCs. Just like in the case of our patients, mammographic and CT scan findings can also be found in other histologically different types of breast cancer, and hence imaging cannot be used alone. The distinction of primary metastases in breast neuroendocrine tumours is vital; the presence of neuroendocrine tumours from another organ should be investigated, in which case the treatment is different [80].

The CT scan findings in our case suggested that the patient has advanced breast cancer with metastasis to the thoracic vertebrae, right scapular blade and spine. With no current management strategies for advanced neuroendocrine breast malignancies, the management principles are currently the same as those of the other types of breast cancers. Therefore, a multimodality therapeutic strategy has been considered, with chemotherapy, endocrine therapy, peptide receptor radionuclide therapy, radiation therapy, surgery, or a combination of the above. In the near future, a better knowledge of the biology of these tumours will hopefully provide new therapeutic targets for personalized treatment.

Due to its rarity, there is not enough evidence to guide specific management, and hence the treatment is that of invasive breast carcinoma of no special type. Further studies are desirable to elucidate the clinical behaviour.

3. 7. Sarcoma of the breast

Breast sarcoma is a rare clinical entity that represents less than 1 % of all breast malignancies and less than 5 % of all sarcomas [81, 82]. The rarity of these tumours limits most studies to small retrospective case reviews and case reports making clinicopathological studies difficult [83]. Sarcomas have a mesenchymal origin and are classified into primary breast sarcomas (de novo) and secondary breast sarcomas, which grow as a result of previous irradiation or chronic lymphedema [84]. Histologically, breast sarcomas can be classified into several subtypes: including fibrosarcomas, pleomorphic sarcomas, leiomyosarcomas, rhabdomyosarcomas, and angiosarcomas [85]. Breast sarcomas typically affect patients aged 55–59 years [86]. The optimal treatment of breast

sarcomas involves a multidisciplinary team which decides on the appropriate management of each individual patient [83, 87].

Case presentation

We report the case of a 73-year-old African female on treatment for systemic arterial hypertension, who presented to our breast oncology clinic with a 3-month history of a rapidly enlarging painful left breast lump. The patient had no previous history of malignancies or exposure to irradiation. Clinical local examination revealed an asymmetry of the breasts, where the left breast was bigger than the right (**Fig. 12**). There was a tumour in the left breast measuring 15 cm × 18 cm, with no skin or chest wall involvement. Axillary lymph nodes were not palpable. Further systemic examination was unremarkable. Mammographic findings revealed a large dense retro-areolar mass with suspicious intralesional calcifications visualized in the left breast (**Fig. 13, *a, b***) and multiple ovoid sub-centimeter axillary lymphadenopathy. Abdominal ultrasonography was grossly normal. The histopathological result of an incisional biopsy demonstrated features of sarcoma showing heterologous chondroid and osseous differentiation. All immunohistochemical stains were negative for MCK, p63, 34Beta E12 and CK5/6. The patient underwent a left mastectomy with sentinel lymph node biopsy. A few days after surgery, the patient was discharged home in good general condition without complications, with appointments for review in the outpatient clinic; she was also referred to the oncologists for subsequent radiotherapy and continuous follow-up. The post-mastectomy histopathological results showed features in keeping with the mixed multinodular, circumscribed, malignant neoplasm with mixed mesenchymal (68 %), spindle cell (30 %) and epithelial (2 %) components. Surgical margins were clear of malignant cells, and lymph nodes did not have any metastatic deposits.

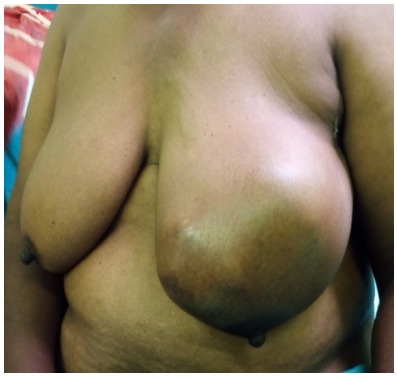
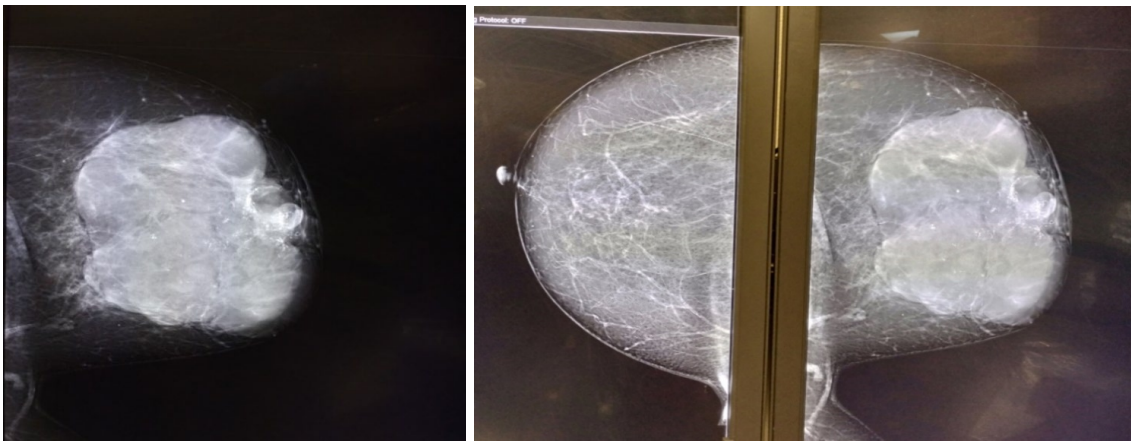


Fig. 12. Breasts asymmetry with the left breast bigger than the right



a *b*

Fig. 13. Mammographic findings: *a* – a large dense retro-areolar mass left breast; *b* – comparison of mammographic findings right & left breast

Discussion

Sarcomas of the breast are a rare and diverse group of mesenchymal-derived malignancies with a unique natural history, treatment, and prognosis if compared to other more common carcinoma-type malignancies of the breast [81]. Although they are rare, they are aggressive, with a high recurrence rate. Unlike most other breast cancers, which spread mainly via a lymphatic system, breast sarcomas usually spread hematogenously. The lungs, liver and bones are the most common sites for sarcomas' metastatic deposits. Sarcomas share some clinical features with breast carcinomas, but the therapy and prognosis can differ substantially [84]. Lymphatic spreads in sarcomas are uncommon; therefore, the nodal status in breast sarcomas is less informative [84]. Breast sarcomas have a high recurrence rate and a poor prognosis [83, 88]. Approximately 80 % of recurrences appear in the first two years [84]. Tumour size, histopathological type, histopathologic grading, the presence of positive margins, and local recurrences appear to be prognostic factors [86].

The most appropriate and effective treatment of breast sarcomas requires a multidisciplinary approach, including experienced sarcoma surgeons, pathologists, radiotherapists, and medical oncologists [83]. Surgical intervention with adequate resections of margins is considered the gold standard of treatment. Negative surgical margins free of malignant cells are more important in terms of local recurrences and overall survival than the extent of surgical resection [83]. There is much debate surrounding the optimal surgical strategy to achieve clear surgical margins. Nevertheless, most sarcoma centres advocate aggressive surgical management with radical or Patey mastectomy rather than breast conservation surgery (BCS) or wide local resection (WLE) [89]. Lo S *et al.* found that WLE in sarcomas was associated with an unacceptably high incomplete excision rate of 87.5 % [89]. There is also controversy concerning the use of radiotherapy or chemotherapy in patients with breast sarcomas, and there is no consensus on this matter, as the use of adjuvant therapies may often depend on the risk of tumour recurrence [84]. Al-Benna S *et al.* recommended the use of neoadjuvant chemotherapy in order to shrink the tumour and help to obtain negative surgical margins [83]. Currently, the use of radiotherapy seems to be recommended in patients with a positive margin resection because the risk of recurrences is high, and in those patients with R0 resections when tumours were larger than 5 cm or a histopathological investigation found a high-grade sarcoma [84, 88].

Local recurrence appears to be higher for breast sarcomas than for sarcomas of other anatomical locations (22 % versus 16 %) which may suggest that more aggressive surgical treatment is required for sarcomas of the breasts [90].

Breast sarcomas are a rare but aggressive type of tumour. The higher the tumour size, the worse the prognosis. Axillary lymph nodes in sarcomas, unlike in other breast cancers, are usually not affected by metastases. The optimal treatment of breast sarcomas requires a multidisciplinary team. Surgery with an adequate resection of margins remains the mainstay of treatment. A close follow-up is strongly recommended because of the high risk of recurrence.

4. Conclusion

Adenomyoepitheliomas of the breast have a risk of recurrences and are best treated with wide local excisions obtaining clear surgical margins. Close follow-ups are essential to assess recurrences and /or malignant transformations.

Invasive micro-papillary carcinoma is a rare, aggressive variant of breast cancer. Its frequent lymph-vascular invasion and high tumour grades correlate with its aggressive nature. However, no significant difference in overall survival has been yet proven.

Primary malignant melanoma of the breast is a rare entity, and diagnosis still follows a thorough, appropriate triple assessment.

Primary Non-Hodgkin's Lymphoma of bilateral breasts is uncommon. It grows rapidly during the antenatal and postpartum periods, especially in the HIV population. Urgent attention is required for prompt investigations of breast lumps in pregnant or postpartum HIV patients, which must be followed with immediate treatment if proven NHL.

Due to the nature of the impairments in individuals with Down syndrome, such as intellectual disability, it may be difficult for early recognition of many conditions, breast cancer included and hence posed an early detection and diagnostic challenge.

Breast sarcomas are a rare but aggressive type of tumour. The optimal treatment of breast sarcomas requires a multidisciplinary team. Surgery with an adequate resection of margins remains the mainstay of treatment. A close follow-up is strongly recommended because of the high risk of recurrence.

Most of these rare cases are presented to the Mankweng Breast Oncology clinic in the advanced stage. Breast cancer awareness campaign is highly important for women in Limpopo, particularly when they come to attend primary health care for any other conditions.

Conflict of interest

The authors declare that there is no conflict of interest in relation to this paper, as well as the published research results, including the financial aspects of conducting the research, obtaining and using its results, as well as any non-financial personal relationships.

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Data availability

Data will be made available on reasonable request.

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