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Synchronous Presence of Chronic Lymphocytic Leukaemia and Breast Cancer in Nigerian Adult Females: Case Series

Ogbo F. O[1], Otu T. I[2,3], Yawe KD. T[1,4], Okpako I. I[1].
[1]Department of Surgery, University of Abuja Teaching Hospital, Gwagwalada, Abuja, FCT, Nigeria
[2]Department of Haematology and Blood Transfusion, Faculty of Basic Clinical Sciences, College of Health Sciences, University of Abuja, FCT, Nigeria.
[3]Department of Haematology and Blood Transfusion, University of Abuja Teaching Hospital, Gwagwalada, Abuja, FCT, Nigeria.
[4]Department of Surgery, Faculty of Medicine, University of Abuja, FCT, Nigeria.

Abstract:- Synchronous presentation of Chronic Lymphocytic Leukaemia (CLL) and Breast Cancer (BC) has been reported, but are uncommon. Although studies have revealed that the risk of second primary malignancies (SPMs) developing in patients with CLL is twice that of general population, it was also noted that concomitant SPMs in untreated BC are very rare[1,2,3,4,5]. Studies have also shown that early diagnosis and appropriate management of malignancies are central to patients' treatment outcome (better quality of life and overall survival) and very poor prognosis and treatment outcome for patients presenting with advanced stage (stage IV) cancers[1,2,3,6,7].Synchronous presentation of CLL and BC, to the best of our knowledge, has not been previously reported in our environment. In this report, we describe our observation of two female patients diagnosed with synchronous primary CLL and BC. This raised a series of diagnostic, etiological and therapeutic issues in a resource poor setting like Nigeria, persuading us to report these rare findings.

Keywords:- *Chronic Lymphocytic Leukaemia, Breast cancer, Second primary malignancies, Synchronous presentation.*

I. INTRODUCTION

Synchronous presentation of Chronic Lymphocytic Leukaemia (CLL) and Breast Cancer (BC) have been reported but are uncommon. Although studies have revealed that the risk of second primary malignancies (SPMs) developing in patients with CLL is twice that of general population, it was also noted that concomitant SPMs in untreated BC are very rare[1,2,3,4,5].Studies also have shown that early diagnosis through the use of primary diagnostic tests (like FBC, bone marrow aspiration and biopsy, fine needle aspiration, incision/excision biopsies); ancillary investigations for confirmatory and prognostic markers and clinical staging (e.g: immunophenotyping chromosomal, cytogenetic, biochemical analyses and imaging), as well as appropriate treatment modalities for malignancies are central to patients' management outcome (better quality of life and overall survival)[1,2,3,6,7,12]. The challenges inherent in management of synchronous primary cancers include: decision on the sequence of treatment (such aswhich of the two cancers should be treated first), the treatment modalities and regimen (radiotherapy, chemotherapy,surgery, immunotherapy, andtargeted therapy; singly or in various combination) and management of the associated co-morbidities and complications[1,7].

CLL is the most common adult leukaemic lymphoproliferative disorder in Western countries with annual incidence of 2 – 4.5/100,000 new cases [4,7]. It is the second most common haematological malignancy after diffuse large B-cell lymphoma in Nigeria, the disorder accounted for 17 – 26.09% of all haematological malignancies, with 2 – 6 per 100,000 new cases diagnosed annually[8,9,10,11]. CLL is characterized by proliferation and accumulation of functionally incompetent mature-looking monoclonal CD5 positive small B lymphocytes in the bone marrow with attendant peripheral blood lymphocytosis > 5 X 10^9/L; infiltration of lymph nodes, spleen and liver. Thus, patients with CLL present with a wide range of symptoms and signs associated with bone marrow failure and/or immune dysfunction such as, infection, anaemia, thrombocytopenia. Although CLL is eventually lethal, its onset is insidious and usually follows a protracted and indolent clinical course, with 25% - 50% of patients being asymptomatic at the time of presentation[7,10]. Breast Cancer (BC) on the other hand, is also the commonest cancer worldwide, it accounted for 22.7% and 37% of all new cancer for both sexes and new cancer cases in females respectively in Nigeria in the year 2018,[12,13,14,15]. BC is characterized by the presence of a painless, hard, irregularly shaped breast lump/s which have different consistence comparing to surrounding breast tissue. The lump may be associated rapid growth, skin erythema, peau d'orange, nipple deviation, nipple ulceration or puckering. There may be associated axillary lymph nodes enlargement at presentation. The breast lesion/s have different biological subtypes when subjected to immunohistological analysis.

Synchronous multiple primary malignancies is the occurrence of two or more cancers within a six months period in the same patient[3]. Although, presence of concurrent multiple primary cancers may be simply due to chance, studies have shown that the etiologies of synchronous multiple primary cancers are multifactorial, dysregulated immune system; shared genetic susceptibility and environmental factors; advanced age; and detection bias due to increased surveillance in patients diagnosed with a primary cancer[2,3]. Most (65.9% - 87%) patients with CLL and BC in resource poor countries are diagnosed in advanced stages due to lack of awareness, and poor access

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to medical care, while in developed countries, where 70% - 80% of CLL cases are diagnosed incidentally inearlystageduring routine complete blood count for unrelated medical check-up, and majority of the BC cases by routine screening. Although, the burden of both cancers are high in developed and underdeveloped countries, the mortality rates of these cancers are very high latter compared to the very low mortality rates in the western countries[7,9,10,12,15,16,17]. Although, high incidence of both CLL and BA have been reported in Nigeria, synchronous presentation of CLL and BC, to the best of our knowledge, have not been previously reported in this environment. In this report, we describe our observation of two female patients affected by primary synchronous CLL and BC. This raised a series of diagnostic, etiological and therapeutic issues in a resource poor setting like Nigeria, persuading us to report these rare findings.

II. CASE REPORT 1

A 61-year-old postmenopausal woman, of Hausa tribe, para 9 and 5 children alive who was referred from Specialist hospital Bauchi State to our Surgery Outpatient Department with a histologically confirmed right breast invasive ductal carcinoma. NST, TxN2M0; and immunohistochemistry result of Oestrogen receptor (ER^{+ve}) positive, Progesterone receptor (PR^{-ve}) and human epidermal growth factor receptor-2 ($HER\text{-}2/neu^{-ve}$) negative tumour with high level of ki67. On detailed medical history, there was no associated weight loss (BMI = 25.8kg/m^2), fatigue, fever or any co-morbidities or other specific complaints. No family history of cancer or exposure to environmental risk factors. Physical examination revealed skin involvement (right breast), peau d'orange and a transverse scar of the previous incisional biopsy that was done in the referral centre. A Matted ipsilateral axillary lymph node enlargement was note, normal left breast, liver and spleen were not enlarged. She had modified radical mastectomy (Auchincloss) done. She did well post operatively and was discharged home after she had the first course of chemotherapy (intravenous Docetaxel and oral capecitabine).

She presented to the clinic for second cycle of chemotherapy, on review of her previous full blood counts, series of elevated white blood count (between 131-148 x 10^9/L) with predominantly lymphocytes and smear cells suggestive of chronic lymphocytic leukaemia (CLL) was noted. Follow-up full blood count result showed, Hb - 11.9g/dl, WBC – 99.9 x 10^9/L, with 90% lymphocytes, smear cells and 10% neutrophils; Platelet count – 302 x 10^9/L. Bone marrow aspirate revealed: Hypercellular marrow with predominantly mature looking small monomorphic lymphocytes (accounted for 90% of the marrow nucleated cells) and numerous smear cells. Mild erythroid hypoplasia with megaloblastic changes; Suppressed myelopoiesis with sequential maturation, few giant metamyelocytes and band forms; Megakaryocytesare adequate in number; Plasma cells not increased in number; No foreign cells seen (Figure 1). Both peripheral blood and bone marrow findings were consistent with diagnosis of CLL. Further secondary confirmatory and prognostic markers (immunophenotyping such as CD5, CD20, CD19 CD23, chromosomal and cytogenetic, and biochemical analyses) workup for CLL were not performed due to lack of the requisite facilities in our center. She was thus, diagnosed as case synchronous CLL (Binet stage A) and BC.

III. CASE REPORT 2

A 52-year-old postmenopausal woman, of Igbo tribe, para 7, all of the children are alive who presented with an overwhelming disease on self-referral to Accident and Emergency Department of our hospital, with three months history of rapidly growing bilateral breasts masses with associated protrusion of the left eye, multiple intra-abdominal masses, swellings on the trunks and gluteal regions, and inability to walk. There is associated fever but no weight loss, A detailed past medical history was taken, which was reported positive for prior use of oral contraceptive pills and primary co morbidities. She was diagnosed with diabetes and hypertension 20 years prior to presentation and has been on regular medications (Amlodipine and Lisinopril). No environmental exposition to risk factors, as well as no family history of cancer.

Physical examination revealed an obese woman (BMI = 35.8kg/m^2), with marked proptosis (>28) of the left eye and chemosis; hyperpigmented surrounding skin, peau d'orange bilateral breasts masses (Figure 2); and bilateral axillary infra and supraclavicular lymphadenopathies. Hepatomegaly, splenomegaly, pelvic masses, gibbus and no associated loss of sensation. Both Right and Left breast biopsy tissues histology reported invasive tubular carcinoma. TNM stage T4cN3M1 with metastasis to the bones, cerebral and liver.

She was evaluated and was noted to have elevated white blood count (43.1 x 10^9/L) with differential leukocyte count: Lymphocytes 90%, smear cells, Neutrophils 7%, Monocytes 2%, Eosinophils 1%. Repeated FBC showed: Hb -8.7 g/dl, WBC – 55.1 x 10^9/l, Platelet count 417 x 10^9/L, the blood smear showed predominance of small lymphocytes and numerous smudge cells. Bone marrow aspirate smear also revealed marrow hyperplasia with predominance of small lymphocytes, numerous smudge cells, markedly suppressed erythroid and myeloid cells series cells, and adequate number of megakaryocytes, no foreign cells seen. Peripheral blood and marrow aspirate findings were consistent with diagnosis of CLL. Patient was diagnosed as synchronous primary CLL (Binet stage B) and BC (stage IV). Patient succumbed to the multiple morbidities before any further secondary investigations could be performed.

Written informed consent for use of their history and investigation results were obtained from both patients as well as ethical approval from the institutional research ethics review board (IRB) of University of Abuja Teaching Hospital, Gwagwalada, FCT, Nigeria.

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IV. DISCUSSION

Patients with CLL have been reported to have increased risk of developing second primary malignancies (SPMs), and breast cancer constitute 9% of these SPMs.[1,2,4,18]. Patients with CLL present with a wide range of symptoms and signs associated with bone marrow and immune dysfunction including infections, anaemia, thrombocytopenia. And onset of the disease is insidious with 25% - 50% of pts being asymptomatic at the time of presentation[7,10]. Most (65.9% - 87%) patients with CLL and BC in resource poor countries are diagnosed in advanced stages due lack of awareness, and poor access to medical care, unlike in developed countries. where 70% - 80% of CLL cases are diagnosed incidentally in early stage during routine complete blood count for unrelated medical check-up or workup for other morbidities, similarly, majority of the BC cases are diagnosed during routine screening (mammography) programs[7,9,10,16,17]. Both of our patients presented with advanced BC, just as reported by various studies. While case report 2 presented with advanced CLL (fever/infection and weakness; lymphadenopathy, splenomegaly, hepatomegalyand, it is important to note that case report 1, has no apparent clinical features of CLL, it was an incidental finding following routine workup for BC. This highlighted the need for diligence by clinicians when reviewing all investigations reports so as not to miss flagged results and appropriate communication from the medical laboratory, despite our busy schedules occasioned by very high patient turnout in our setting. The megaloblastic changes observed in her marrow aspirate could be attributed to the antimetabolite capecitabine in her chemotherapy regimen. However, folate and vitamin B_{12} (nutritional) deficiencies have been shown to cause anaemia in CLL and should be ruled out, she is thus, being evaluated appropriately.

V. DIAGNOSIS

Ancillary investigations for confirmatory and prognostic markers and clinical staging are crucial in the determination of initiation of therapy and treatment modalities in current cancers management globally. Sadly, most resource poor countries (including Nigeria) have to contend with lack of requisite facilities for secondary investigations in most of the public health care institutions. The high cost of these ancillary tests in the few public and private diagnostic centers couple with the limited health insurance coverage in the country makes these essential tests inaccessible to majority of cancer the patients. Thus, physicians in these setting face the challenges of making the best use of primary and the few ancillary diagnostic tools available as documented in the case reports. The incidental diagnosis of CLL, following review of previous FBC results on subsequent follow up visit, highlights the need for comprehensive review of all tests reports and surveillance for the presence of second primary cancer(s) in patients diagnosed with a primary cancer by clinicians.

VI. MANAGEMENT

Thorough primary and ancillary assessment of cancers patients could mitigate or help in resolving most of the challenges inherent in the management of synchronous primary malignancies. The treatment modalities and regimen are, Surgery; Radiotherapy; Chemotherapy; Hormone; Immunotherapy; Targeted therapy; (singly or in various combination); with other supportive care. The clinical features, genetic, molecular and biochemical characteristics of the cancers can help in the determination of the sequence of treatment, treatment regimen and anticipate management complications. When both cancers require treatment, the therapy should be targeted to the more aggressive cancer[1,7]. CLL is a chronic disease with insidious onset, patients who are asymptomatic (Binet stages A and B, or Rai stages 0 - II with no associated B symptoms) do not require treatment, but are routinely followed-up until the disease progresses, death in these patients may be due to an unrelated cause, therapy should be initiated for patients with Binet stage C or Rai stages III and IV[7]. Treatment is recommended once BC diagnosis is established. Our first case report patient had modified radical mastectomy (Auchincloss)and first cycle of chemotherapy (intravenous Docetaxel and oral capecitabine). Marked reduction in patient's pretreatment lymphocyte count from 148 x 10^9/L to 99.9 x 10^9/L during the follow-up visit was noted, this might be attributed to the effect of the chemotherapy. She is currently on second line chemotherapy using Docetaxel and oral capecitabine combination regimen. The second patient diagnosed with advanced stage (Binet stage C and stage IV) synchronous CLL and BC succumbed to her multiple morbidities before any further secondary investigations could be performed or treatment initiated.

VII. CONCLUSIONS

We report two female patients diagnosed with synchronous primary CLL and BC, This rare synchronous presentation of CLL and BC, to the best of our knowledge, has not been previously reported in our environment. One of the objectives of this report is to alert physicians in our setting on of the need for surveillance to improve the detection of uncommon malignancies. We highlighted diagnostic, etiological and therapeutic issues encountered in a resource poor setting like Nigeria and the need to: Create public awareness of the prevalence of cancers and importance of early diagnosis through routine screening programs for common cancers that are curablein our environment; Equip tertiary health institutions with the requisite secondary diagnostic facilities for effective efficient cancer workups that are imperative for identification of genetic and epigenetic factors associated with cancerprognostication; And advocate wider health insurance coverage to enable all cancer patients access these facilities.

- **Conflict of interest:** The authors have no conflict to declare.
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- **Correspondence:** Dr .Felix Ogili Ogbo, michellad34@gmail.com

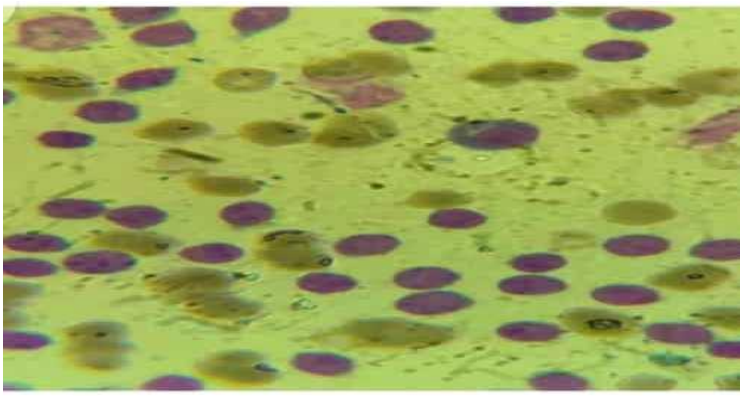

Fig. 1: Bone marrow Aspirate from case 1

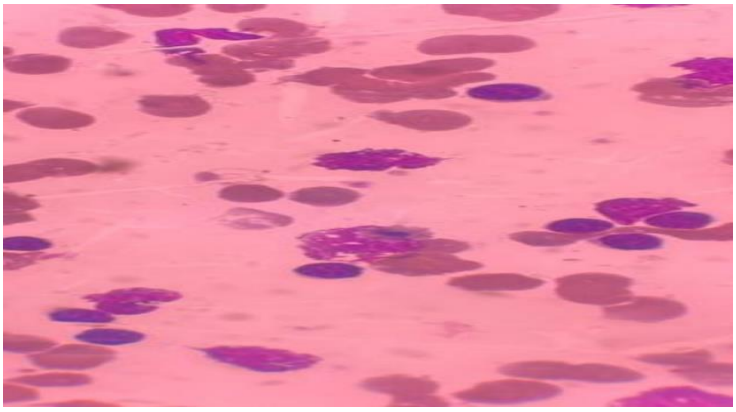

Fig. 2: Bone marrow Aspirate from case 2.

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