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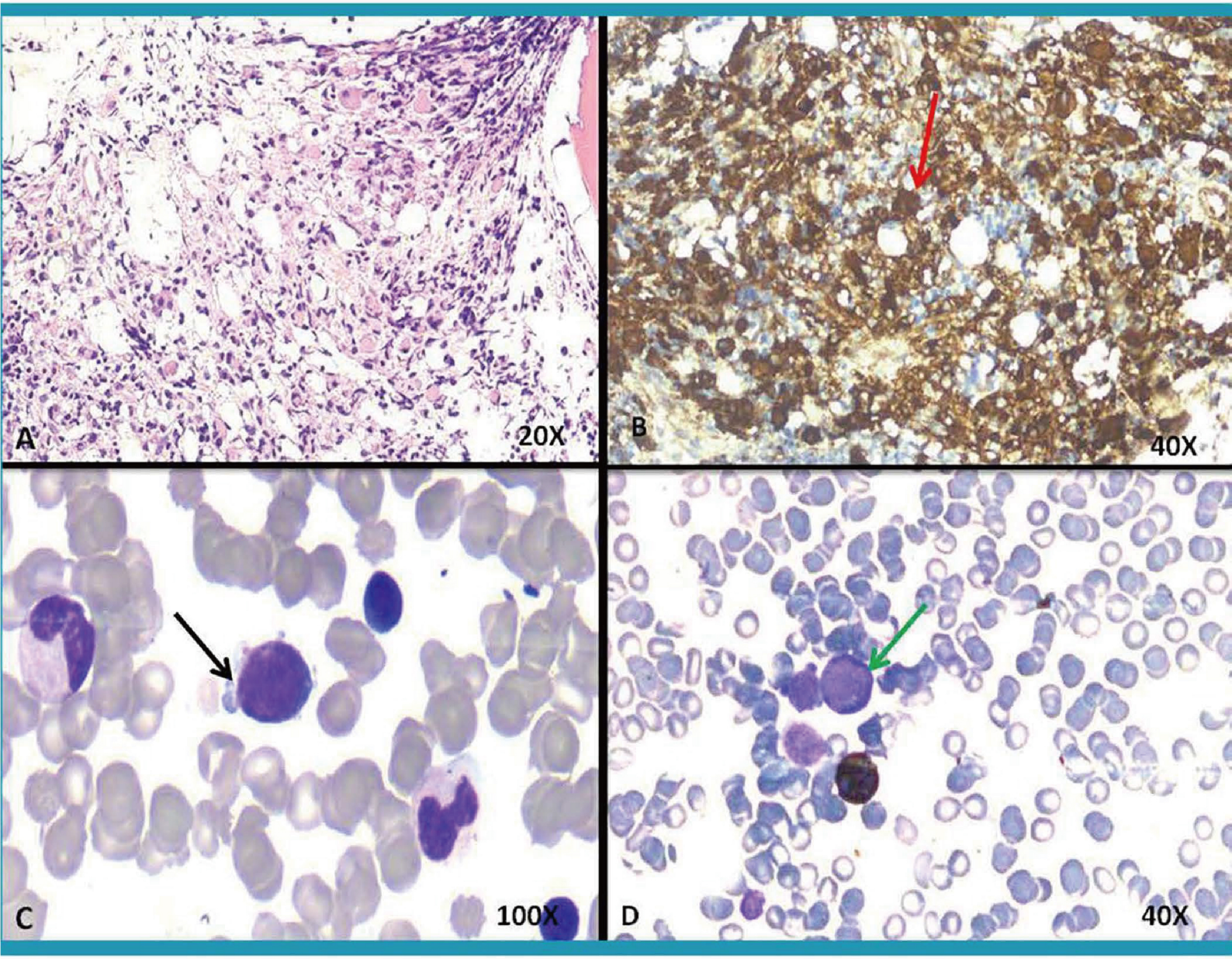

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Current Cancer Reports

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CORRESPONDENCE

Curr Cancer Rep, 2022, 4(1): 128-132
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REVIEW

Breast cancer in women in the Democratic Republic of the Congo: Current state of knowledge

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Abstract: Breast cancer (BC) is a major health problem with an increasing trend in prevalence and mortality worldwide. It is the most common of female cancers in the world, and thus ranks first in both developed and developing countries. Current knowledge on the epidemiology and biological aspects of breast cancer in women in the Democratic Republic of the Congo remains insufficient and poorly documented. Given the trend towards urbanization of the Congolese population, it is likely that current data will change in the coming decades, due to a foreseeable change in risk factors for the disease. Therefore, the establishment of a cancer registry is necessary in the Democratic Republic of the Congo (DRC) health system for better epidemiological monitoring of cancer and surveillance data necessary for the development of cancer control policies and their integration into primary health care. Strategies that include building local capacity in terms of human resources, equipment and technology transfer could lead to new concepts and therapies adapted to the Congolese geographical context.

Keywords: breast cancer, epidemiology, women, Democratic Republic of the Congo (DRC)

1 Introduction

Breast cancer (BC) is a major health problem with an increasing trend in prevalence and mortality worldwide. It is the most common of female cancers in the world, and thus ranks first in both developed and developing countries. It accounts for 23% of female cancers and 10.9% of all human cancers worldwide [1]. By 2020, according to recent estimates by the World Health Organization (WHO), there were 2.3 million women with BC and 685,000 deaths from BC worldwide. By the end of 2020, 7.8 million women alive had been diagnosed with BC in the past five years, making BC the most common cancer in the world. Globally, women lose more years of life (disability-adjusted life expectancy) due to BC than any other type of cancer [2]. Over the past two decades, epidemiological reports published in different parts of the world show a significant increase in BC mortality [3]. BC is present in all countries of the world and affects women of all ages from puberty (although the incidence rate increases as age progresses) [2].

BC is one of the leading causes of cancer deaths in Africa and has the highest incidence of all cancers. Although BC is the most common cancer among women worldwide, fatality rates are highest in low- and middle-income countries [4]. There are few data on BC in Africa in general and Central Africa in particular. Of 46 WHO Member States in sub-Saharan Africa (SSA), only 20 (43.4%) have active cancer registries, covering a wide range of coverage and completeness [5, 6]. In 2018, a recent meta-analysis conducted in 22 African countries by Adeloye *et al.* [6] noted significant variations in the reported incidence of cancer in women between population and hospital cancer registries. These authors found that in hospital records, the overall combined incidence rate was estimated to be 23.6 per 100,000 person-years (95% confidence interval [95% CI]: 18.5-28.7). North Africa and the SSA had relatively comparable rates of 23.2 per 100,000 (95% CI: 6.6-39.7) and 24.0 per 100,000 (95% CI: 17.5-30.4), respectively. The overall aggregated incidence of BC from population-based registries was 24.5 per 100,000 (95% CI: 20.1-28.9). The incidence of SSA was lower at 22.4 per 100,000 (95% CI: 17.2-28.0) than in North Africa at 29.3 per 100,000 (95% CI: 20.0-38.7). In East and West Africa, the incidences were 28.0 (95% CI: 21.7-33.7) and 24.2 (95% CI: 15.4-33.0) per 100,000, respectively. Southern Africa had an incidence of 19.0 (95% CI: 10.1-27.8), while Central Africa had an incidence of 13.4 (95% CI: 7.2-34.1) per 100,000. These authors found

that incidence rates increased significantly between 2000 and 2015 in both registries [6]. This meta-analysis reported that the mean age ranged from 30.6 to 60.8 years, with over 33% and 81% of the population aged 30 to 49 years and 30 to 59 years, respectively [6]. According to Jedy-Agba *et al.* [7], many cases of BC in SSA are diagnosed between 35 and 49 years of age, and many patients have presented with advanced BC.

2 Breast cancer situation in the DRC

According to recent estimates (July 2020), the total population of the Democratic Republic of the Congo (DRC) is estimated at 101,780,263 inhabitants, i.e. a density of 43.36 inhabitants/km^2 [8]. The population of the DRC is very young: half the population is under 15 years of age. Those over 65 represent less than 3% of the country's total population [9]. The rate of urbanization, i.e. the urban population as a proportion of the total population of the DRC, increased from 28.8% in 1970 to 30% in 1984, to 32% in 2007 [10]. The 2020 estimate is 45.6%. Urbanization continues at a rate of 4.53% per year [8]. The mortality rate in the general population is estimated at 8.4 deaths per 1,000 population. Life expectancy is 61 years in the general population (59.3 years for men and 62.8 years for women); access to basic health services is 28.7% (28.5% in urban areas and 28.7% in rural areas) [8]. In the DRC, there are few data on cancer in general due to the lack of a national cancer registry that would collect all data from hospitals and non-governmental organizations. Since November 2020, the DRC has had a National Center for the Fight against Cancer (CNLC) which serves to support cancer control. A number of initiatives are being undertaken by both the State (by integrating the fight against cancer into the national budget) and the private sector (for example by providing the country with a radiotherapy center). Histopathology and immunohistochemistry laboratories were established.

In 2006, a study reported that BC was the most common cancer among women in Kinshasa [11]. According to WHO data from 2014, 30,700 people die each year from different types of cancer in the DRC. More than 55% are women and cervical cancer (27%) and BC (16%) were the top two [12]. Mashinda *et al.* [13], in their survey from 1969 to 2008 based on the registers and protocols of biopsies consulted in the pathological anatomy laboratories of the Kinshasa University Clinics and the General Reference Hospital in Kinshasa, found that cancers of the cervix (27.7%) and of the breast (13.7%) were the most prevalent in women. During the 10-year period from June 2010 to June 2020, 5,801 cases of cancer (all sexes) were recorded in five pathological anatomy laboratories in Kinshasa, Katumbayi *et al.* [14] recorded 3,163 cancers in women, of which BC was predominant (49.9%). Lukanu *et al.* [15], in a recent study of 914 cancer patients at IME-Kimpese Hospital, the only hospital in Central Kongo Province with a histopathology department, reported that the breast was the most affected organ with 26.3% of cases and mainly in women (234/240).

As regards the characteristics of patients with BC, a study carried out with 430 cases in 3 hospitals in the city of Kinshasa (Saint Joseph Hospital, Kinshasa Provincial Reference General Hospital and Nganda Hospital Center) during the period from 1 January 2005 to 31 December 2015 reported that the mean age of 48.5±10.2 years, lymph node invasion was encountered in 66.3% and 94.4% of the patients had consulted at advanced stages (III and IV) [16]. As for the immunohistochemical aspects of BC, in a series of 50 women with BC, Mbala had found that estrogen and progesterone receptors were detected in 86% and overexpression of the human epidermal growth factor receptor 2 (HER2) was absent in 90% of the cases [17].

3 Difficulty in diagnosis and care in sub-Saharan Africa and the DRC

Successful treatment stems from the multi-pronged approach to this disease, with improved treatment options over decades. Management of BC has evolved rapidly over the last 15 years, thanks to a better understanding of tumor biology. Several types of treatment such as immunotherapy, vectorized chemotherapy, hormone therapy sensitized with mammalian target of rapamycin (mTOR) inhibitors were discovered and implemented. They are thriving and are commonly referred to as "targeted therapies". During the latter, the treatments are personalized and administered according to the tumor molecular profile of each patient [21, 22]. A judicious combination of systemic therapy (including the use of chemotherapy, hormone therapy, targeted or molecular therapy and immunotherapy alone or in combination) and local therapy with radiotherapy and/or surgery when indicated is the best approach for BC patients [23]. Invasive BC involves a heterogeneous group of patients and therefore is very difficult to manage. Thus, an individualized approach is necessary to achieve good results [22, 23].

In developed countries, for nearly two decades, the incidence and mortality of BC has been declining, thanks in particular to screening allowing earlier diagnosis, the control of certain modifiable risk factors (*e.g.* reduced prescribing of hormone replacement therapy, smoking cessation, reduced alcohol consumption, physical activity, reduced sedentary status, reduced overweight, adoption of a diversified and balanced diet, *etc*.) and recent significant therapeutic advances (in both adjuvant and metastatic situations) [22,24]. These major advances in the management of BC include targeting hormone receptors and HER2, knowledge of the mechanisms of hormone resistance and coupling chemotherapy to an anti-HER2 antibody (TDM-1) increasing its selectivity towards cancer cells and improving its tolerance [16].

In developing countries including the DRC, there is no national strategy for cancer control planning, which requires information on the precise diagnosis of cancer and documentation of all prognostic factors relevant to a tumor. Accurate diagnosis requires timely and adequate pathological input [25]. Diagnosis remains the cornerstone of treatment. Even advanced cancer requires confirmation of breast carcinoma by pathological diagnosis, as other benign or malignant tumors can mimic BC, for example lymphoma, phylloid tumor or untreated infection, and all these treatment approaches merit different treatment approaches [26]. However, current reports show a significant gap in professional and technical pathology services, with low pathologist/population ratios in SSA [27]. These ratios in SSA vary from one pathologist for 84,133 people in Mauritius to one pathologist for 9,264,500 people in Niger. For the DRC, this report indicated that this ratio was of one pathologist to 4,938,733 persons [27]. In addition, countries such as Somalia, Benin, Eritrea and Burundi have only one or no pathologists in the country [28].

In addition to this lack of pathology, most patients in SSA have advanced disease (stage III and IV) [7, 29–33]. The goal of the WHO's new global initiative on BC control is to reduce BC mortality worldwide by 2.5% per year, and thus prevent 2.5 million BC deaths globally between 2020 and 2040. The achievement of these objectives is based on three pillars: health promotion for early detection; timely diagnosis; and comprehensive management of BC [2]. But this achievement comes up against several obstacles in developing countries. The challenge of timely and accurate diagnosis of BC is even greater in low-resource areas such as the DRC where access to pathological investigations is not guaranteed. Coverage of basic laboratory services is fundamental to achieving these objectives. Yet comprehensive laboratory services are not available for large percentages of the SSA population. In addition, several other factors may also contribute to the difficulty of correctly diagnosing BC in the context of limited resources. These include clinical manifestations that are varied and appear late due to the lack of systematic screening and lack of information on BC among some healthcare workers and the general public (lack of awareness of BC symptoms and their severity, fear of a cancer diagnosis, use of traditional healers), lack of access to health care services (due to geography, financial concerns, quality of services) [27, 29, 34, 35]. Thus, most of the time, treatment is initiated on the basis of an imprecise and/or late diagnosis which results in the use of inappropriate treatment. The latter in turn leads to a long hospital stay with an increase in the costs of care initially already expensive in a community where 70% of the population lives below the poverty line, a bad evolution of BC with local and remote metastases (lungs, liver, bone, brain) and death (Figure 1). As a result, most women in SSA are undergoing mastectomy and hormone therapy or adjuvant chemotherapy (sometimes not indicated) and many others are receiving only palliative care because the tumor is advanced and inoperable [32].

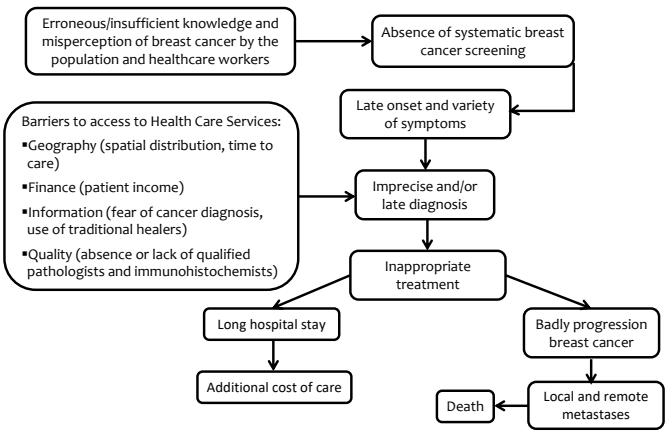

Figure 1 Conceptual model of the breast cancer management problem in low-resource settings

4 Conclusion

Although BC is the most common cancer in women, very few studies have been conducted in the DRC where current knowledge of the BC epidemiology remains inadequate and poorly documented in women. However, to address women's health problems, advanced epidemiological studies are essential for policy makers, public health experts and program managers. Therefore, the establishment of a cancer registry is necessary in the DRC health system for better epidemiological monitoring of cancer and surveillance data necessary for the development of cancer control policies and their integration into primary health care. Hence the involvement of strategies including the strengthening of local capacities in terms of human resources, equipment and technology transfer is very crucial. This is very important for the development and strengthening of national guidelines for the management of BC in Congolese women in general.

Abbreviations

BC: Breast cancer
DRC: Democratic Republic of the Congo
HER2: human epidermal growth factor receptor
SSA: sub-Saharan Africa
WHO: World Health Organization

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CASE REPORT

A case of life threatening acute Nivolumab induced autoimmune haemolytic anaemia

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Abstract: Autoimmune haemolytic anemia is a rare but potentially catastrophic adverse event of immune checkpoint inhibitor therapy. We present the case of a gentleman who presented with non-specific symptoms while undergoing adjuvant Nivolumab therapy after potentially curative surgery for gastroesophageal cancer. The patient's haemoglobin deteriorated to 4.7 g/dl with no evidence of bleeding and serologic tests indicative of hemolysis. He received emergent massive RCC transfusion receiving 9 units of bloods in 1 night, and was commenced on high dose methylprednisolone. During subsequent weeks of inpatient care, the patient continued to received multiple daily red cell transfusions and had a total of 53 RCC transfusions during admission, along with high doses of steroids,4 doses of weekly Rituximab as well as 2 doses of IVIG. While he was discharged on day 38 of admission, he required a slow taper of steroids over 6 months. Immune related hemolytic anemias are a rare corollary of immune check point inhibitors. The cases of immune related AIHA documented in the literature were treated with steroids, Rituximab and IVIG, which are also recommended by guidelines for the treatment of immune related haemolytic anemias.

Keywords: autoimmune haemolytic anemia, Nivolumab, hemolysis, hematologic toxicity, immunotherapy, immune related toxicity

1 Introduction

Immune checkpoint inhibitors (ICI) have revolutionised the treatment landscape in oncology during the past decade. These agents have been extensively developed for the treatment of patients with metastatic cancer and are now increasingly used in pre and post operative curative cancer settings. However patients treated with ICI are at risk of developing several immune related adverse events, with endocrine, dermatologic, gastrointestinal and pulmonary toxicities being commonly described [1–3]. Autoimmune hemolytic anemia remains a rare but potentially catastrophic adverse event of ICI therapy [4–6]. We present the case of a gentleman who presented with life threatening acute autoimmune hemolytic anemia after receiving adjuvant nivolumab therapy after potentially curative surgery for gastroesophageal cancer.

2 Case

The patient had initially presented with locally advanced, moderately differentiated adenocarcinoma of the distal oesophagus complicating Barrett's oesophagus.

He was treated with neoadjuvant chemoradiation using the CROSS (paclitaxel/ carboplatin) protocol [7]. The patient subsequently had a minimally invasive oesophagectomy. Pathology assessment demonstrated a residual ypT3 ypN1 tumor. The patient was then enrolled on the Checkmate 577 trial (NCT 02743494) which was a global, randomized, double-blind, placebo-controlled phase 3 trial assigning patients to receive adjuvant nivolumab or placebo for one year. This treatment was complicated by occasional episodes of hypoglyceamia despite carbohydrate loading due to postoperative gastrointestinal changes, and to balanitis. Treatment was otherwise

well tolerated up until completion of 1 year of study treatment. CT Thorax, abdomen and pelvis at the end of the treatment period showed no evidence of metastatic disease.

Approximately two weeks after his final cycle of the study drug, the patient presented acutely with a three day history of headaches, fatigue, pyrexia, muscle aches and decreased exercise tolerance. On admission, he was diaphoretic. Vital sign assessment demonstrated that he was afebrile and normotensive with a heart rate of 87, respiratory rate of 15 breaths per minute and normal oxygen saturation (Table 1). Initial admission blood tests demonstrated a haemoglobin of 13.6 g/dl, white cell count of 6.6×10^9/L, C-reactive protein of 66 mg/dl and total bilirubin 23.6 μmol/L. SARS-CoV-2- testing was negative. Radiographs of the chest and abdomen were normal. He was commenced on empiric co-amoxyclavulanic acid for pyrexia of unknown origin but remained febrile and was escalated to Piperacillin-Tazobactam therapy within 24 hours, along with addition of Valacyclovir.

Table 1 Vital signs of patient at admission

Vital sign	Value
Heart rate	87 bpm
Respiratory rate	15 bpm
Oxygen saturation	100%
Temperature	36.8°C
Blood Pressure	128/70 mmHG

In the ensuing days, fever persisted, and jaundice and fatigue developed Antibiotic therapy was broadened with gentamicin. Blood cultures were negative for infective organisms. On day 4 he suffered an episode of loss of consciousness. Repeat testing for SARS CoV 2 was negative. Urgent repeat testing demonstrated a Haemoglobin of 4.7 g/dl without clinical evidence of active bleeding,haematocrit 0.140 L/L, a reticulocyte count of 70×10^9/L, and an elevated lactate dehydrogenase level of 1504 U/L. He was subsequently admitted to the intensive care unit. Attempts to obtain compatible blood products were challenging due to extensive hemolysis (Figure 1) and he initially received 9 units of red cells overnight. Given his acute decline and high likelihood of autoimmune haemolytic anaemia (AIHA), methylprednisolone 1 gram was administered in the early hours of the morning of day 5 of admission. Serological testing showed direct antiglobulin testing was 4+IGG and 3+ C3d-. The trial team were urgently contacted and the patient was unblinded revealing that he had been receiving nivolumab therapy.

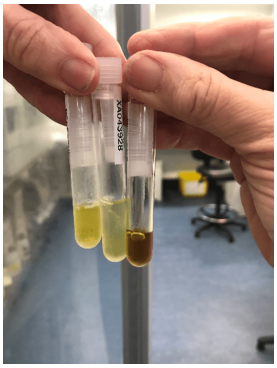

Figure 1 Patients Serum sample with severe haemolysis on the right hand side versus two normal serum samples

The American Society of Clinical Oncology (ASCO) 2018 guidelines on management of immune related adverse events were consulted [8] and he was commenced on methylprednisolone 2mg/kg/day. He continued to receive red cells aiming initially for a haemoglobin $>$ 10 g/dl and subsequently 7 g/dl. Given the low reticulocyte count and slow bone marrow recovery despite folic acid and high dose steroids, a bone marrow biopsy was performed on day 6 of admission. Erythroid precursors represented 50% of total nucleated cell count. There was marked erythroid precursor without megakaryocyte change, consistent with active haemolysis.

Due to persistent fevers,antibiotic therapy was escalated to meropenem for one week on day 10 of admission. Daily lactate dehydrogenase, reticulocyte count and bilirubin were monitored. Methylprednisolone dose was initially decreased to 1mg/kg on day 8, but needed to be increased again to 2 mg/kg after a further 6 days. It was then reduced to 1 mg/kg day 18 of admission, then switched to oral prednisolone 1 mg/kg/day day 28 of admission and this began to be slowly tapered from day 36 of admission. This was supplemented by weekly rituximab for four doses commenced on day 7 of admission and intravenous immunoglobulin 1 mg/kg/day over two days,

on days 13 and 14 of admission. The patient's antibiotics were stopped on day 17 of admission as patient was no longer thought to have an active infection.

The rate of hemolysis and resultant drop in haemoglobin was initially rapid (Figure 2). As the patient was felt to be peri-arrest, he was transfused a group specific rather than fully cross matched unit of RCC in order to commence the transfusion emergently. Red cell transfusion requirements were initially high with AI requiring on average 5 units of red cells daily and on one occasion received 9 units of red cells in a single day. This requirement slowly reduced over a five week period (Figure 3). He received 53 units of red cells in total during admission. Nasojejunal feeding was initiated between weeks 2 to 5 of admission to maintain appropriate calorie intake as well as for its association with improved physiologic and gut function and improved patient outcomes. Physiotherapy was initiated to reduce the impact of deconditioning and steroid associated proximal myopathy. The patient was discharged home on day 38 of admission. At the time of discharge his HB was 8.8 g/dl without needing recent transfusions and he was clinically well and vitally stable.

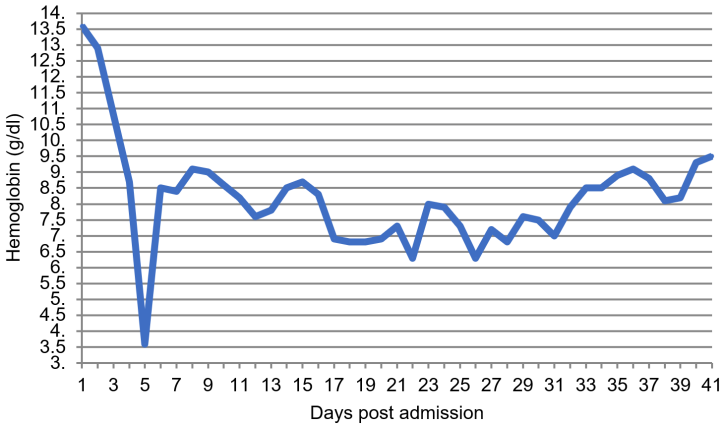

Figure 2 Patient's hemoglobin level (g/dl) during hospital stay

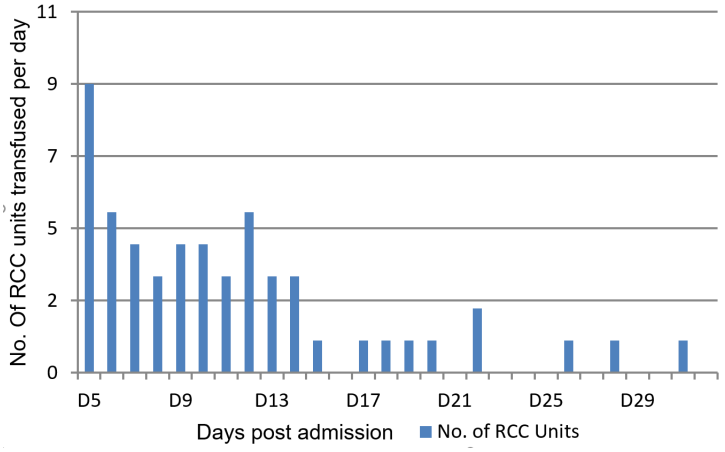

Figure 3 Daily RCC transfusions received by patient during hospital stay

The patient's clinical course post discharge was marked by ongoing hemolysis which required a cautious and slow taper of steroids. Steroids continued on a slow taper of nearly 4 months after discharge during which his haemoglobin slowly improved to 13 g/dl, and his reticulocyte count returned to normal. The patient remained clinically well, and was continued on folic acid as well as prophylaxis for opportunistic infections with Co-Trimoxazole during this time. He subsequently remains well and in remission.

3 Patient perspective

In the month before admission to hospital I began to notice my legs had become increasingly tired. I was not worried about this as my work was physically demanding and I was on my feet for most of the day. I felt a sense of relief when I received my final treatment in that month. I felt well and had experienced few side effects apart from some minor skin irritations. Having no obvious side effects made me question if I was receiving the placebo or the trial drug nivolumab.

At the beginning of the month that I was admitted to hospital, I went golfing with my son. I began to sweat profusely and felt very weak while on the golf course. I returned to the car to rest and have a snack as I thought my blood sugar may be low. We came home and I rested and felt fine for a few days. The following Friday morning I woke up again sweating profusely: the bed sheets were saturated. My wife checked my temperature I had a low grade temp and took two panadol. She then contacted the GP and trials team and I was advised to attend the Accident and Emergency Department. I had a negative COVID test which this brought a huge sense of relief as that was my biggest concern at the time. I was admitted as I continued to sweat and have a temperature I also began to feel very lethargic. I was not overly worried as I thought I had some kind of infection and hoped to be home again in a few days.

As the weekend progressed I felt my condition continue to deteriorate. On the Sunday morning as I attempted to go to the bathroom I fainted and was incontinent of urine. The nursing staff assisted me back to bed as I could not stand up. I was very frightened upset and embarrassed. I rang my wife and told her there was something seriously wrong and I did not know what was happening to me. She then became very worried and felt helpless as she could not visit due to COVID restrictions.

I have no memory of what unfolded in the following days. I was later told that my family were called into the hospital in the early hours of Tuesday morning as my condition continued to deteriorate and I was in a critical condition. I have no recollection of any of these events and I do not remember my family by my bedside.

I have some vague recollection of waking up in intensive care an environment which felt very alien to me. I felt panicked as I did not know what had happened to me and why I ended up there. I found the intensive care environment very upsetting and stressful. I was later moved to the Coronary Care Unit which eased my tension somewhat. I do not know how long I was in Coronary Care as each day rolled into the next. My medical team kept me informed at all times and gave me ample opportunity to ask questions however I was too weak to comprehend the enormity of the situation.

Thankfully my wife was allowed to visit on a daily basis while I remained in a critical condition. I thought about my own mortality on more than one occasion my wife and I spoke about it openly which I found very comforting. I was never in denial about the seriousness of my situation but I never gave up hope.

There was a sense of relief when I was transferred to the ward however this relief was edged with nervousness due to the COVID surge in the community and the hospital. My family were no longer allowed to visit but I was delighted that I was well enough to communicate on the phone. I was elated the morning my consultant told me I was being discharged and I immediately called my wife to collect me.

I have very mixed emotions when I reflect on this experience. I am very thankful that I survived such an event but I also feel a certain amount of anger that I was one of the very few to develop such a rare side effect to this drug. I do not regret having participated in the trial as I am hopeful I will benefit from it in the long term.

4 Discussion

The incidence of AIHA is approximately 100-300 per million per year, with a prevalence of approximately 170 per million [9]. Drug induced immune haemolytic anemias are rare, occurring in 1 in 1 million of the population [10]. Medications including antibiotics such as cephalosporins and penicillins have been thought to cause AIHA, with a 2009 article reporting Cefotetan, Ceftriaxone and Piperacillin as the most common causes of drug induced immune haemolytic anemia [10, 11]. With the advent of ICIs, there have been multiple cases reported of AIHA secondary to their use [4]. The mechanism this is thought to take place is by random activation of the immune system resulting in formation of autoantibodies, activation of T cell clones, and diminished regulatory T cells [4].

Hemolytic anemias remain a rare corollary of the use of ICIs. One estimate of the frequency of AIHA secondary to ICIs put the figure at less than 0.1% or possibly 0.05% [4]. An analysis showed that only 0.211, 0.146, and 0.245 percent of patients suffered from AIHA secondary to treatment with nivolumab, pembrolizumab and atezolizumab respectively [4]. It also reported that out of 12 cases of AIHA secondary to ICI, 8 patients had been on nivolumab while an additional 2 had a combination of nivolumab and ipilimumab [4]. A French study assessed hematologic immune related adverse events secondary to ICI, noted that out of 35 patients, 9 patients (26%) had AIHA [5]. Severity of the adverse event was grade 3 in 1 patient and grade 4 in 8 patients [5]. The study also observed that all of these 9 patients had direct anti-globulin positive with 6 patients with positive C3d and 3 patients with positive IgG. Our patient similarly

had direct antiglobulin test positive with positivity for IgG and C3d. Our patient also underwent a bone marrow biopsy to further investigate his condition. Bone marrow biopsy has been recommended in the literature as part of the workup for an autoimmune haemolytic anemia in selected patients to rule out a lymphoproliferative disorder [11].

AIHA is a decompensating acquired hemolysis that develops as a result of the body's own immune system targeting antigens found on red blood cells with complement activation associated as well [12]. It is characterised as primary when no underlying disease is present. Secondary AIHA is commonly associated with a variety of conditions including lymphoproliferative disorder, autoimmune diseases, congenital syndromes and deficiencies as well as a number of medications as in this case [9]. The T-lymphocyte system plays an important part in the pathogenesis of AIHA, with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) playing a role in immune tolerance [13]. Pharmacologic inhibition of PD-1 as with Nivolumab, therefore, leads to an increased risk of developing AIHA. In terms of management, the recently updated ASCO guideline on management of immune related adverse events recommends the use of high dose steroids as Prednisolone 1-2 mg/kg per day as first line therapy [14]. They also recommend that in case of no improvement, the use of immunosuppressive drugs, such as rituximab, IVIG, cyclosporine and infliximab should be considered [14]. In the present case the patient was treated aggressively with frequent blood transfusion, high dose of steroids along with four doses of weekly rituximab and 2 doses of IVIG. This corresponds to the management of other patients detailed in the literature. An analysis of patients reported in the literature with AIHA secondary to ICI showed that of 12 cases reported, 11 were treated with steroids, 3 received rituximab and 1 received IVIG [4]. The analysis showed that while most patients responded to treatment, the condition was fatal in 2 of 12 patients. Another analysis of AIHA cases from 3 French registries showed that out of 9 patients with AIHA, 4 required steroids only while 5 required additional treatment with rituximab [5].

The results of the Checkmate 577 trial have recently been published [15]. The median disease free survival was 22.4 months as compared to 11 months in favor of nivolumab. These results are practice changing and have led Nivolumab to become a standard of care in this population. Grade 3 or 4 adverse events of any cause occurred in approximately 34% of patients on nivolumab and approximately 32% of patients on placebo. About 13% of patients on nivolumab in the study experienced grade 3 or 4 treatment related adverse events. The most common grade 3 or 4 adverse events were fatigue, diarrhoea, rash, pruritus and raised aspartate transaminase (AST) [15]. Hematologic immune related adverse events were not described as part of the results, which illustrates how rare these adverse effects are.

In conclusion, we detail the case of a patient with severe AIHA secondary to ICI. The agent was given in the adjuvant setting as part of a clinical trial and the AIHA was life threatening, rapid in onset and occurred after treatment was completed. Such events may well become more frequent as ICI become established agents in the adjuvant setting in cancer care, and more patient receive therapy with them. While this patient's case was ultimately successfully managed it was challenging with respect to the rate of onset of symptoms, to the insidious nature of presentation, to the magnitude of the refractory fall in hemoglobin, and to the prolonged and significant degree of blood product support.

Conflict of interest

The authors declare that there is no conflict of interest.

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RESEARCH ARTICLE

Women's breast cancer risk factors in Kinshasa, Democratic Republic of the Congo

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Abstract: **Purpose**: Breast cancer (BC) is the most common malignancy and the leading cause of cancer-related deaths among women worldwide. Risk factors for this disease are numerous and their prevalence varies according to racial and ethnic groups and geographical regions. Therefore, we sought to identify BC risk factors in the Congolese population. **Methods**: A case-control study was conducted at the Nganda Hospital Center in Kinshasa, Democratic Republic of the Congo. One hundred and sixty patients with breast cancer (cases) were compared to 320 women who did not have BC (controls). STATA version 16 was used to analyze data with statistical significance considered at $p < 0.05$. **Results**: There is a strong association between BC in Congolese women and early menarche age (adjusted odds ratio [aOR] = 2.3; 95% CI: 1.2-4.3), family history of BC (aOR = 2.5; 95% CI: 1.2-5.5), overweight (aOR = 1.8; 95% CI: 1.1-2.7), and obesity (aOR = 7.3; 95% CI: 4.0-13.4). **Conclusion**: Our results indicate the presence of certain conventional risk factors. Thus, these results will be of great value in establishing adequate evidence-based awareness and preventive measures among the Congolese population.

Keywords: breast cancer, risk factors, Congolese women, Kinshasa

1 Introduction

Breast cancer (BC) is the most common cancer among women worldwide, in general [1], and in the Democratic Republic of the Congo (DRC), in particular [2, 3]. Numerous epidemiological studies over the past three decades have identified a number of risk factors associated with BC [4–6]. In addition to genetic and reproductive factors, the BC risk varies widely ethnically and geographically [7]. BC risk factors may vary from region to region of the world and environmental factors are more important than genetic factors [6, 8]. One study found that menstrual and reproductive factors are associated with an increased BC risk because they may increase lifetime exposure to estrogen [9]. BC is a multi-factor process. Some authors have focused on genetic predisposition and its association with modern lifestyle, including diet and alcohol consumption [8]. Oral contraceptive pills have also been shown to increase the BC risk, which decreases after discontinuation [10, 11].

In the DRC, with a huge variation in lifestyles, culture, geography, habits, and diets, to our knowledge, there are no publications on BC risk factors. Indeed, factors responsible for differences in the incidence of BC among women are not fully understood, which may be explained by reproductive and lifestyle factors such as diet, menarche, and menopausal age, age at first birth, obesity, abortion, and BC family history [6, 12–15].

Knowledge of risk factors for BC is very important in screening women at risk and in the use of BC screening and prevention programs. Since risk factors are unique to each community, we believe that studying BC risk factors among Congolese women is an important step in planning screening and prevention programs. This study attempts to identify some of different BC risk factors among Congolese women living in Kinshasa, in the DRC.

2 Materials and methods

This was a case-control study of 160 women (cases) aged 26 to 75 who had been diagnosed histologically with primary breast cancer between January 2014 and December 2019, taken care

of in the oncology department of the Nganda Hospital Center in Kinshasa (DRC). This center is recognized as a reference center for BC management in the DRC. During this study period, women with BC received a letter of introduction describing objectives of the study. Women who agreed to participate in the study were then interviewed personally by a qualified interviewer.

The control group consisted of 320 Congolese women with no BC history or neoplastic disease and were invited to participate in the study questionnaire. These volunteers were recruited into the study during the same calendar period as cases. The control women were recruited from the same city as cancer patients. The case-control ratio was 1:2. Cases and controls were matched individually with age ($\pm$ 2 years).

The questionnaire included information on age, current body mass index (BMI), physical exercise status, smoking, alcohol consumption, personal history of diabetes mellitus, family history of BC, and reproductive characteristics such as age at menarche, parity, breastfeeding, and use of oral contraceptives. In addition to the BMI (which was based on actual measures of weight and height), all other factors studied here were self-reported. Informed consent was obtained from study subjects prior to the interview.

Data entry and analysis were performed using Epi Info 7.2 and STATA version 16. Bivariate and multivariate analyzes were performed and adjusted odds ratios [aOR] (by logistic regression analysis) were calculated. The p-value of <0.05 was considered statistically significant.

3 Results

A total of 480 women (160 BC cases and 320 controls) participated in the study. Table 1 presents the distribution of demographic characteristics and potential risk factors studied between cases and controls separately. No statistically significant differences were observed in the age distribution of cases and controls (p=1,000). The mean age of cases and controls was 43.4 $\pm$ 11.6 years and 42.7 $\pm$ 10.9 years respectively (p = 0.525).

Table 1 Age and potential risk factors for participants

Variable	Cases (n=160) n (%)	Controls (n=320) n (%)	p-value
Age			1.000
$<$ 40 years	28 (17.5)	51 (15.9)	
40-49 years	56 (35.0)	119 (37.2)	
50-59 years	44 (27.5)	90 (28.1)	
$\geq$ 60 years	32 (20.0)	60 (18.8)	
Age at menarche			0.022
$<$ 12 years	24 (15.0)	25 (7.8)	
$\geq$ 12 years	136 (85.0)	295 (92.2)	
Parity			0.716
0	19 (11.9)	33 (10.3)	
$\geq$ 1	141 (88.1)	287 (89.7)	
Breastfeeding			0.336
Yes	138 (86.3)	287 (89.7)	
No	22 (13.8)	33 (10.3)	
Oral contraceptive use			0.505
Yes	150 (93.7)	306 (95.6)	
No	10 (6.3)	14 (4.4)	
Alcohol consumption			0.303
Yes	125 (78.1)	264 (82.5)	
No	35 (21.9)	56 (17.5)	
Smoking			1.000
Yes	5 (3.1)	9 (2.8)	
No	155 (96.9)	311 (97.2)	
Body mass index (kg/m^2)			$<$ 0.001
$<$ 25	63 (39.4)	202 (63.1)	
25-29.9	53 (33.1)	98 (30.6)	
$\geq$ 30	44 (27.5)	20 (6.3)	
Physical activity			0.244
No	27 (16.9)	70 (21.9)	
Yes	133 (83.1)	250 (78.1)	
Family history of BC			0.008
No	142 (88.7)	306 (95.6)	
Yes	18 (11.3)	14 (4.4)	

No statistically significant differences between cases and controls were observed in terms of parity, oral contraceptive use, alcohol consumption, smoking, breastfeeding, and physical activity (p$>$0.05). In contrast, significantly higher proportions of cases than controls reported for

family history of BC (11.3% versus 4.4%), early menarche (15.0% versus 7.8%), overweight (33.1% versus 30.6%), and obesity (27.5% versus 6.3%).

Table 2 presents odds ratios (and 95% confidence intervals [95% CI]) for BC risk based on characteristics of each participant after adjusting for the effect of all variables in a multivariate model. Strongest associations were observed with family history of BC, menarche age, and BMI; these associations persisted after adjustment for the effect of all other factors. The aOR for the family history of BC was 2.5 (95% CI: 1.2-5.5).

Table 2 Multiple logistic regression of breast cancer risk factors in women

Variable	aOR [95% CI]	*p*-value
Age at menarche		
$<$ 12 years	2.3 [1.2-4.3]	0.011
$\geq$ 12 years	1.0	
Family history of BC		
Yes	2.5 [1.2-5.5]	0.020
No	1.0	
Body mass index (kg/m^2)		
$<$ 25	1.0	
25-29.9	1.8 [1.1-2.7]	0.014
$\geq$ 30	7.3 [4.0-13.4]	$<$ 0.001

A statistically significant trend with age at early menarche and BC risk was also observed; women who started menstruating before the age of 12 had an increased risk of BC compared to women who started menstruating later, even after adjusting for the effect of all other risk factors (aOR = 2.3; 95% CI: 1.2-4.3). For BMI, we noted that women who were overweight (aOR = 1.8; 95% CI: 1.1-2.7) and obese (aOR = 7.3; 95% CI: 4.0-13.4) had a significantly elevated risk of BC compared to those with normal BMI.

4 Discussion

The etiology of BC is still poorly understood and known risk factors for BC account for only a small proportion of cases. Epidemiological studies in different populations have identified a range of well-established and probable BC risk factors [16, 17]. These include age, socioeconomic status, reproductive events, breastfeeding, BC family history, and lifestyle. However, most of epidemiological studies on BC involve subjects living in North America and Western Europe, regions that represent only a fraction of the world's population. Therefore, there is a need for further research on the epidemiology of BC in populations in less well-studied regions of the world, in order to better understand the etiology of BC [17]. This is the first epidemiological study on the risk factors for BC in the Congolese population.

The identification of women at high risk of developing BC is very important to prevent the onset of the disease. Because of the paucity of data among Congolese women, we decided to assess here the strength of the association between recognized risk factors and BC among Congolese women. Thus, well-established risk factors for BC identified in other populations, such as family history of BC, early menarche age, and overweight/obesity, had strongest associations with BC risk among Congolese women.

Comparing the BMI between cases and controls, there is a statistically significant difference between the two groups. Women who were overweight (aOR = 1.8) and obese (aOR = 7.3) had a significantly higher risk of breast cancer compared to those with normal BMI. Our data support the concept that obesity is a significant risk factor for disease, consistent with previous studies of different populations in different regions [18–21]. Overweight/obese women have reduced progesterone levels because obesity can cause anovulation and decreased progesterone production during the luteal phase. Obesity also increases endogenous estrogen levels and decreases sex hormone binding globulin, which increases free estradiol levels [7, 22]. According to García-Estévez *et al.* [23], the association between BC risk and obesity (overweight/obesity) varies with menopausal status. Some studies reported a negative correlation between obesity and BC risk in premenopausal women [24, 25]. In our study, no information on the status of menopause at the time of diagnosis was available. Elkum *et al.* [21] reported that the BC risk was significantly higher in overweight or obese Arab women before and after menopause. This significant association between obesity and BC risk was not found in the study by Hadjisavvas *et al.* [4].

In this study, we have shown that the BC family history is an independent predictor of BC. Women with a positive BC family history had an approximately three-fold increased risk of BC (aOR = 2.5). This is consistent with what has already been reported in various populations

in different geographic regions [4, 21, 26]. This also reflects the role of genetic and epigenetic modifications on important genes such as BRCA1 and BRCA2 in disease predisposition [27].

Our results showed that early menarche age is a risk factor for the BC development. Cases were more likely than controls to have had menarche before age 12 (aOR = 2.3). The BC risk is associated with several reproductive factors. It is well established that the BC risk increases with early menarche age [4, 12, 28]. This association is consistent with the hypothesis that the BC risk is related to the extent of mitotic activity of the breast. This activity is driven by estrogen and progesterone exposure during the luteal phase of the menstrual cycle [29], which determines the probability of tumorigenic somatic events [30]. As a result, early menarche age increases the period during which the breast is mitotically active and subsequently increases the BC risk. Like previous researchers, we have observed that an early age at menarche is associated with a high BC risk in our population.

The interpretation of our results should take into account certain limitations. First, because the study is cross-sectional, it precludes any relationship between outcomes and associated factors. Second, factors studied were based on respondent reports, except for the BMI, which was measured only once for cases and controls. Third, another limitation of this study was the inability to assess certain factors, e.g., hormone replacement therapy, early delivery at advanced age, education level, marital status, socioeconomic level, and medical history such as diabetes mellitus, diet, which would have been associated with BC. The future study should include these variables.

5 Conclusion

This study presents the first report on BC risk factors among Congolese women. Strongest associations with the BC risk in the Congolese population were observed with BC family history, early menarche, and overweight/obesity. Overall, these results support results of previous surveys of the descriptive epidemiology of BC risk factors. There is a need for more targeted prevention and early diagnosis campaigns among the Congolese population.

List of abbreviations

95% CI: 95% confidence intervals
aOR: adjusted odds ratio
BC: breast cancer
BMI: body mass index
DRC: Democratic Republic of the Congo

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RESEARCH ARTICLE

Epidemiological and histopathological features of ocular tumors in Bukavu, Democratic Republic of the Congo

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Abstract: Purpose: To describe epidemiological and histopathological features of ocular tumors observed in two ophthalmology departments in Bukavu in the Democratic Republic of the Congo. **Methods:** A cross-sectional descriptive study and a simple proportion analysis were performed to describe the epidemiological and histopathological characteristics of 103 consecutive anatomical pieces taken after tumor removal from two ophthalmology services in Bukavu city from January 2018 to December 2020. **Results:** Children accounted for 40% of patients and ocular tumors were unilateral in 84.5% of cases. The most common locations were the retina (34.8%), conjunctiva (33.7%) and eyelids (22.8%). Benign tumors predominated (51.4%), followed by malignant tumors (37.9%), and undetermined tumors (15.5%). The main histological forms found were retinoblastoma (34.8%), conjunctival nevus (20.6%), and palpebral granuloma (16.3%). **Conclusion:** Ocular tumors are common in Bukavu. Histopathological examination remains essential to guide management to reduce the risk of recurrence and related complications.

Keywords: ocular tumor, histopathology, retinoblastoma, Bukavu

1 Introduction

Ocular tumors are neoplasms developed at the expense of the eyeball, its adnexa, and orbit. They may be benign, pre-malignant, or malignant, occurring without distinction of race, sex, or age [1]. Ocular tumors are rare and their hospital frequency varies considerably from one study to another. Ocular tumor disease is more common in Africa than in developed countries [1,2].

Malignancies compromise the functional prognosis of the eye and the life-threatening prognosis of the affected patient. Their early diagnosis is essential, based on histopathological examination for appropriate management [3]. Diagnosis of malignancies is most often difficult, especially in developing countries, where they are clinically and histologically confusing. Histopathology is the standard of excellence for diagnosis, however, it is not without difficulties, as diagnosis can often vary from one pathologist to another [4]. A regular anatomical-clinical confrontation, involving pathologists, ophthalmologists, radiotherapists, and oncologists is essential for optimal diagnostic accuracy and therapeutic management [5].

While benign nature remains the most common of ocular tumors, some of them have a risk of malignant transformation [6], therefore, a good knowledge of their clinical and pathological characteristics is necessary in order to detect suspicious lesions and to offer a suitable treatment without compromising the patient's vital, functional and aesthetic prognosis. This practice implies a rigor in order not to treat benign lesions excessively and above all not to treat malignant lesions by default, with the risk of putting at risk the functional and vital prognosis of the patient [7]. In most cases, diagnosis is based on the clinical picture(less reliable), mainly because there is a shortage of histopathology services in most developing countries. However, even in countries where these services are available, about half of lesions are not histopathologically tested [4]. Indeed, some common ocular tumors are well known; some rather exceptional ones pose a number of diagnostic and therapeutic problems in many ophthalmology services in developing countries for several reasons [5] including: late consultation at a time when tumors are already threatening the patient's functional and even vital prognosis, lack of infrastructure, lack of qualified personnel,

lack of adequate diagnostic and therapeutic means, as well as the poverty of the population which makes paraclinic investigations and expensive treatment financially inaccessible.

In a study conducted in Dakar (Senegal), retinoblastoma was found more frequently, accounting for 66.6% of all oculo-orbital tumors and 95.45% of tumors in the eyeball [8]. Benign tumors are more frequently located at the ocular surface, compared to malignant tumors, represented by squamous cell carcinoma, lymphoma, and melanoma [9]. Among the palpebral tumors, basal cell carcinoma is by far the most common, compared with epidermoid and muco-epidermoid carcinoma, sebaceous carcinomas and Merkel cell carcinomas [10].

The objective of this study was to describe epidemiological and histopathological features of ocular tumors observed in two ophthalmology services in Bukavu, in the Democratic Republic of the Congo (DRC).

2 Materials and methods

2.1 Study setting and design

This is a cross-sectional descriptive study of consecutive biopsies taken from patients with ocular tumors in the ophthalmology service of the General Referral Hospital of Panzi and the ophthalmological clinic CELPA-CBM in Bukavu city (in the Democratic Republic of the Congo), over a three-year period from January 2018 to December 2020.

2.2 Study population

This study included all biopsies from the two ophthalmology services listed above during the study period; 103 biopsies were examined. The analysis data were collected on a sheet prepared for this purpose.

2.3 Pathological analysis of biopsies

2.3.1 Macroscopic examination

Biopsy samples were classified into two categories: enucleation pieces with suspicion of retinoblastoma and all other biopsies. All biopsy samples collected were fixed in 10% formalin solution. They were then systematically subjected to macroscopic examination and microscopic examination according to an established protocol.

The enucleation pieces, taken in case of suspicion of retinoblastoma, were received in the laboratory, preferably in the fresh state and oriented with sutures. The sample was weighed, measured by large and small diameter. The segment of the optic nerve was examined and measured. The fixation was carried out using a 10% formalin solution. For the attachment of the intra-orbital compartment components, 1 ml of intraocular fluid was removed with a syringe and replaced with an equivalent volume of 10% formalin solution. The duration of fixation was 24 hours to 48 hours maximum.

The first sample fragment was a terminal section slice of the optic nerve that was completely included in a cassette. Then, a posterior sagittal section of the eyeball from the optic nerve to the cornea was formed to maintain a ratio between the optic nerve and the tumor and expose the tumor. The tumor was endophytic in nature when it developed towards the optic nerve. It was exophytic in nature when it developed posterior with optic nerve invasion; and it was diffuse as it invaded in both directions. The size, color, size, consistency, and location of the tumor were specified. The detachment of the retina was sought.

All enucleation were included in full and at least 10 cassettes were prepared.

Other biopsy samples, other than enucleation, were received in the laboratory, fixed in 10% formalin solution, and generally oriented with suture. The macroscopic examination examined the size (in all three dimensions), shape, consistency and color of each piece. The internal macroscopic examination examined the section slice and specified the color and existence of outbreaks of hemorrhage, necrosis or other alterations. Samples of 2 mm thick biopsy sections were taken and placed in coating cassettes. These sections were dehydrated in a series of alcohol baths, thinned with xylol, impregnated in paraffin heated to 57 °C, and then included in paraffin blocks. Microtomous sections of 3-5 μm thick strips were then made. These ribbon segments were then mounted on object-carrying blades previously coated with albumin. After drying in the oven, preparations were subjected to the basic coloration, hemalin-eosin.

2.3.2 Microscopic examination

All histological sections were subjected to double reading by optical microscope, by two experienced pathologists, first at 5X and 10X magnification for a focus and a panoramic view of the microscopic field; and then at 40X magnification for finding and describing lesions.

For enucleation pieces with suspicion of retinoblastoma, the positive microscopic diagnosis was based on the presence of small-undifferentiated round cells with cytonuclear atypies and mitoses. The presence of rosettes in the form of Flexner-Wintersteiner and Homer-Wright bodies made it possible to specify the degree of differentiation. Necrosis and calcification sites were sought. Histoprognostic elements were infiltration of the choroid (superficial or deep), sclera or optic nerve and its meningeal sheaths, subretinal space, iris, lens, ciliary body, or anterior chamber.

For other biopsy pieces, the microscopic description of lesions was made and the conclusion was consistent with the diagnosis that was recorded on a previously established data sheet.

2.4 Data analysis

Data entry and analysis were done on the SPSS software version 16. Analysis and interpretation used the calculation of the proportion.

3 Results

Out of 103 patients who consulted for ocular tumors, 39.8% were aged 15 or less and 24% were over 45 years old. Females were predominant (51.5%). Ocular tumors were unilateral in 84.5% of the cases and the left eye was the most affected (47.6%) (Table 1).

Table 1 Distribution of patients by age, sex and side

Variable	Number (n = 103)	Percentage (%)
Age		
0-15 years	41	39.8
16-30 years	13	12.6
31-45 years	16	15.5
46-60 years	24	23.3
> 60 years	9	8.7
Sex		
Male	50	48.5
Female	53	51.5
Side		
Right eye	38	36.9
Left eye	49	47.6
Both eyes	16	15.5

Figure 1 shows the distribution of ocular tumors according to their histological nature and it is apparent that, among the 103 biopsy samples analyzed, 39 (37.9%) corresponded to malignant tumors and 53 (51.4%) were benign.

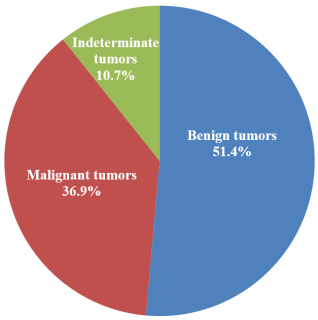

Figure 1 Distribution of ocular tumors by histological nature

In terms of anatomical location, retinal tumors predominated (34.8%) followed by conjunctival tumors (33.7%) and palpebral tumors (22.8%). Among benign tumors, conjunctival tumors accounted for 54.7%. In addition, retinal tumors accounted for 82% of all malignant tumors (Table 2).

Of the total of 92 tumors, retinoblastoma was the most represented tumor (32/92 or 34.8%), followed by conjunctival nevus (19/92 or 22.8%) and palpebral granuloma (15/92 or 16.3%). Conjunctival nevus (35.8%) and palpebral granuloma (28.3%) were the most common histological types of benign tumors. Retinoblastoma (82%) was the most common type of malignant tumor (Figure 2).

Malignant tumors predominated in children (82.1%), while benign tumors were distributed in all age groups at proportions below 27% (Table 3).

Table 2 Types of tumors according to their anatomical location

Anatomical location	Malignant	Benign	Total
Eyelid	3 (7.7%)	18 (34.0%)	21 (22.8%)
Conjunctiva	2 (5.1%)	29 (54.7%)	31 (33.7%)
Retina	32 (82.1%)	0 (0.0%)	32 (34.8%)
Orbit	2 (5.1%)	6 (11.3%)	8 (8.7%)
Total	39 (42.4%)	53 (57.6%)	92 (100.0%)

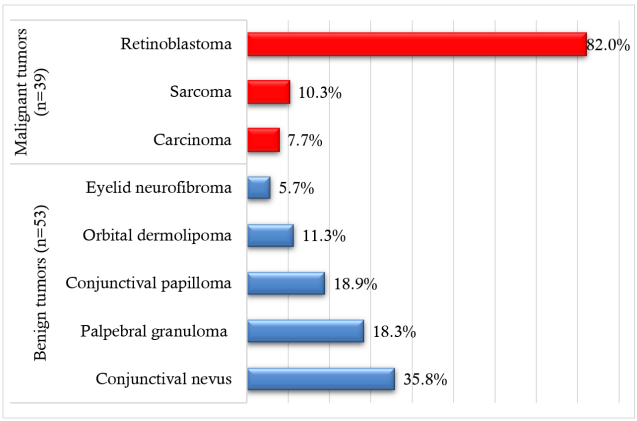

Figure 2 Distribution of ocular tumors by histological type

Table 3 Distribution of ocular tumors by histopathological nature and age of patients

Age	Malignant	Benign	Total
0 - 15 years	32 (82.1%)	9 (17.0%)	41 (44.6%)
16 - 30 years	0 (0.0%)	13 (24.5%)	13 (14.1%)
31 - 45 years	1 (2.6%)	14 (26.4%)	15 (16.3%)
46 - 60 years	3 (7.7%)	11 (20.8%)	14 (15.2%)
$>$ 60 years	3 (7.7%)	6 (11.3%)	9 (9.8%)
Total	39 (42.4%)	53 (57.6%)	92 (100.0%)

4 Discussion

This study described the demographic characteristics of 103 patients with ocular tumors in Bukavu (in the DRC). Females predominated and accounted for 51.4% of patients with a female-to-male ratio of 1.1. Similarly, Levecq *et al.* [6], in a study carried out in Belgium, had found female predominance. Contrary to our results, several authors found male predominance without any explanation [2,5]. This observed sex difference is due to the difference in sampling techniques used in these studies.

Children aged 0-15 were the majority, accounting for 39.8%. The same is true of results of earlier studies which found that ocular tumors are more common in subjects aged 0 to 15 years and that within the same age group, those under 10 years are more affected [11].

The present study had shown that in 84.5% of the cases, ocular tumors were unilateral and they were located on the retinal gland (34.8%), the conjunctiva (33.7%), the eyelid (22.8%), and the orbit (8.7%). Kasongo *et al.* [11], in their study conducted in Lubumbashi (in the DRC) mentioned the preponderance of unilateral tumors (86.5%) and the retina was the most affected anatomical site (41.9%) followed by conjunctiva (37.8%). The same is true in Antanonarivo (Madagascar) where Volamarina *et al.* [12], had shown that 93% of ocular tumors were unilateral and that palpebral localization was noted in 60% of cases. Adnexal localization (conjunctival and palpebral) was reported in several studies [2,4,5,13,14]. Sylla *et al.* [15] showed a predominance of bilateral lesions.

Of the 103 biopsy specimens analyzed in our study, 53 (51.4%) were benign tumors, 39 (37.9%) were malignant tumors and 11 (10.7%) were indeterminate tumors. This predominance of benign tumors was also reported by Nkodo *et al.* [2] in Yaoundé (Cameroon) which had 61.1% benign tumors. This finding is contrary to that reported by several authors who recorded a predominance of malignant tumors between 49.5% and 62.2% [4,5,11,15]. Discrepancies observed between our results and those in the literature could be explained not only by a biopsy recruitment bias; but also by the existence of a not insignificant proportion of indeterminate tumors (10.7%), a consequence of histological inaccuracies.

Conjunctival nevus (35.8%) and palpebral granuloma (28.3%) were the most common histological types of benign tumors in this study. The most common benign tumors appear to vary by author. Some authors had found a predominance of inflammatory pseudotumors [1, 2], for others it was pterygion [11, 16], hemangiomas [4], or conjunctival nevus [17]. These differences may be due to biopsy recruitment bias.

In our study, retinoblastoma (82%) was the most common histological type of malignancies. Many authors unanimously present retinoblastoma as the most common malignant tumor ranging from 30 to 85% [1, 2, 4, 5, 11, 16, 17].

In our series, malignant tumors predominated in children (82.1%). Our results emphasize that retinoblastoma is a tumor almost exclusively of the child (0-5 years) and extremely rare in adults and are consistent with those of the literature [18–20].

5 Conclusion

This study provided valuable information on ocular tumors in Bukavu. The most common locations were the retina, conjunctiva and eyelids. Benign tumors predominated (51.4%), followed by malignant tumors (37.9%), and indeterminate tumors (15.5%). Major histological forms found were retinoblastoma, conjunctival nevus, and palpebral granuloma. However, histological precision of indeterminate tumors would provide more detail. This is why histological analyzes should be made available for better management orientation, in order to reduce the risk of recurrence and related complications.

Authors' contribution

The authors confirm the contribution to the paper as follows: study conception and design: BBM, OM, PBK, ZKT, SOW, TBK, RBC; data collection: BBM, DBK, EHN, RHN, TBK; analysis and interpretation of results: BBM, OM; draft manuscript preparation: BBM, OM, ZKT, SOW, TBK, RBC. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest.

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CORRESPONDENCE

Black-White disparities in fatigue and comorbidity among breast cancer survivors

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Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning [1]. A common side effect of cancer treatment with chemotherapy or radiation therapy, fatigue has an adverse effect on several areas of functioning including mood, physical function, cognitive performance, work performance, and social interaction [1].

Among breast cancer survivors, fatigue is one of the most frequently reported and distressing symptoms [2]. Breast cancer survivors have reported more intense and more frequent fatigue than their counterparts without a history of cancer [2–4]. Cancer-related fatigue impairs the quality-of-life of cancer survivors and their ability to return to work [2, 5, 6]. Fatigue generally improves after therapy is completed, but some level of fatigue may persist for months or years following treatment [1]. In a subset of patients, fatigue may be a significant issue long into survivorship [7, 8]. Cancer-related fatigue is common in long-term survivors who no longer suffer from cancer itself [5]. Longitudinal studies are needed to understand the course of cancer-related fatigue over time [2].

The mechanisms responsible for cancer-related fatigue are only partially understood. In addition to cancer treatment, multiple psychological distress, sleep disturbance, cardiac problems, and immunological factors may have a role [1]. Factors that contribute to fatigue include cancer treatment, anemia, hormonal therapy, psychological distress, depression, sleep disturbances, smoking, and concomitant medical illness (e.g., congestive heart failure, diabetes, or obesity) [1, 2]. Younger breast cancer survivors have been reported to be more likely to have cancer-related fatigue than older women [2]. Aromatase inhibitors, which are used as adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer, have been associated with cancer-related fatigue [1].

Fatigue is a common finding among diabetic patients [9]. Diabetes has been associated with worse fatigue among both breast cancer patients and women without a history of breast cancer [10]. In breast cancer patients, diabetes has been thought to exacerbate cancer-related general and mental fatigue during chemotherapy and into survivorship [10]. A higher BMI, as with obesity, has also been associated with greater self-reported fatigue [11]. Obese breast cancer patients have been found to have significantly higher cancer-related fatigue at baseline and at 6 months post-chemotherapy as compared to non-obese breast cancer patients [12].

Black-White disparities in fatigue and comorbidity among breast cancer survivors are also important to consider. In general, Black adults have significantly higher rates of diabetes and obesity than other racial groups [13, 14]. As compared to White breast cancer patients, Black breast cancer patients have also been found to have higher rates of diabetes and obesity, as well as obesity-related comorbidities, hypertension, and hyperlipidemia [14, 15]. Further, Black patients are more likely than white patients to gain weight and shift to a higher BMI during chemotherapy for breast cancer [16]. Black breast cancer survivors are also less likely to engage in physical activity, which is a risk factor for cancer-related fatigue [17].

Cancer-related fatigue presents with considerable variability among patients that is not explained by factors related to the disease or treatment, suggesting that there

may be biological, behavioral, or psychosocial factors that affect its trajectory [18]. Black breast cancer survivors have been found to have worse mental, general, and physical fatigue ratings than White breast cancer survivors [19]. While White survivors demonstrate improved emotional and general fatigue from diagnosis to 6 months post-treatment, Black survivors do not display this trend [19].

This variability in cancer-related fatigue among Black and White breast cancer survivors may be partly due to the increased rates of obesity and diabetes among Black patients since both factors can exacerbate cancer-related fatigue. It is important to understand the role of these factors in cancer-related fatigue because cancer-related fatigue strongly predicts the quality of life of breast cancer survivors [2]. To reduce the burden of diabetes and obesity on cancer-related fatigue, recommendations for glycemic control and weight loss should be made to breast cancer survivors with underlying diabetes or obesity, respectively [10, 12].

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