Challenges managing women with suspected Lynch Syndrome in Zimbabwe: a case report

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Introduction

LS is a common hereditary cause of endometrial, colorectal, ovarian and other extracolonic carcinomas (breast, gastric, skin, renal tract and pancreatoco-biliary). It is caused by germline mutation of mostly five deoxyribonucleic acid (DNA) mismatch repair (MMR) genes (mutS homolog 2 [MSH2], mutL homolog 1 [MLH1], mutS homolog 6 [MSH6], postmeiotic segregation 2 [PMS2] and postmeiotic segregation1 [PMS1]). Some 90% of cases are due to mutation in the MLH1 and MSH2 MMR genes. Most women with LS develop a gynaecological malignancy as their sentinel cancer, with the risk of developing endometrial cancer exceeding the risk of developing colorectal cancer.2,3

Women with LS have an up to 40–62% and 4–12% lifetime risk of developing endometrial and ovarian carcinomas respectively,4,5 and the gold standard for diagnosis is germline molecular testing. Tumour immunohistochemistry (IHC) can be utilised to triage women who need to undergo germline molecular testing. In Zimbabwe these tests are unavailable and there is therefore no data on the prevalence of LS.

We now discuss the challenges faced in managing a woman with suspected LS-associated endometrial carcinoma.

Case presentation

Mrs SB, a 56-year-old retired nurse who is para-five, presented to the Gynaecology Outpatients Department at Parirenyatwa Hospital in Harare with a three-month history of heavy post-menopausal bleeding (PMB). Her menarche and menopause were at the ages of 16 and 49 years respectively. There was no history of use of hormone replacement therapy and she had well-controlled chronic hypertension. A Pap smear done at presentation was normal.

She underwent treatment for an adenocarcinoma of the ascending colon, T2N1M0, at the age of 41 years. Adjuvant treatment was not indicated, so she had close surveillance only and was discharged after five years of follow-up and remains disease free.

Mrs SB had a strong family history of colorectal carcinoma (CRC). Her mother died at the age of 48 and her eldest daughter died at the age of 32, both from CRC. Mrs SB had no family history of extra-colonic malignancies and had never smoked, but occasionally consumed alcohol.

On clinical examination she was alert and fully conscious with no jaundice, pallor or lymphadenopathy. Her blood pressure, pulse and temperature were 125/81 mmHg, 92 bpm and 36°C respectively; she was obese with a BMI of 38 kg/m². On abdominal examination, paramedian and transverse right lower quadrant surgical scars were noted from the previous CRC surgery and appendicectomy respectively. Her abdomen was soft and non-tender, and no pelvic-abdominal masses were palpable. Pelvic examination showed normal external genitalia, vagina and cervix; uterus 12/40 in size; and no adnexal masses were palpable. A pelvic ultrasound scan (US) showed a bulky uterus measuring 9.2 cm in length, with an abnormally thick endometrium measuring 19 mm. Endometrial sampling was done with a manual vacuum aspiration (MVA) syringe using a size 4 mm Karman cannula. Histology results showed grade 2 endometrioid adenocarcinoma.

Haemoglobin count, mean cell volume and platelet count were 9.7 grams/dL, 79.3 fl and 414 000/L respectively; urea and creatinine levels were 4.3 mmol/L and 84 umol/L respectively. She was screened for diabetes mellitus and HIV and both tests were negative.

This case was discussed in a multidisciplinary team (MDT) meeting and the grade 2 endometrioid adenocarcinoma was confirmed on histopathology review. The review of her chest X-ray and abdominal US did not show any metastatic disease. The tumour board recommended surgery including lymph node dissection.
Mrs SB’s surgery was delayed by industrial action by public sector healthcare workers, whereupon she opted to have the surgery at a private hospital where a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and bilateral pelvic lymph node dissection were carried out. On the final histopathology report, the tumour was downgraded to a grade 1 endometrioid carcinoma, confined to the inner half of the uterus (Figure 1) with no cervical involvement and both adnexae were not involved. The lymph nodes were not evaluated due to financial constraints.

Her case was reviewed in an MDT meeting and the final stage was FIGO IA, grade 1 endometrioid endometrial carcinoma. The MDT meeting recommended follow-up only. Her uterine specimen was sent to the Lancet Laboratory in Cape Town, South Africa for IHC (performed without charge). The results displayed partial loss of expression of MSH2 with complete loss of expression of MLH1 and PMS2 (Figure 2). This is in keeping with microsatellite instability (MSI)-high which is observed in 90% LS associated carcinomas. The patient could not afford germline molecular testing to confirm the diagnosis, so a presumptive diagnosis of LS was reached based on the IHC results.

The patient recovered well from the surgery and she was agreeable to the MDT plan for follow-up only and remains disease free. Her children were invited for counselling and they indicated that they were not able to afford screening.

**Discussion**

LS is an autosomal dominant, highly penetrant, germline mutation disorder that predisposes women to colorectal, endometrial and other extracolonic malignancies. Mutations in MMR genes are responsible for this syndrome. MMR genes code for MMR proteins, which recruit repair enzymes to correct damaged DNA by excising the incorrect DNA sequence to allow correct resynthesis of the sequence by DNA polymerase. A mutation in the MMR genes results in their inactivation, causing MSI. Microsatellites are short-tandem DNA repeats that occur in coding and non-coding genes and when unstable are prone to expansion or contraction – the instability which can cause an abnormal gene expression. MSI is characteristic of DNA replication errors and is the hallmark of a number of LS-associated tumours.

A strong clinical suspicion usually arises from a strong personal and family history of LS-associated malignancies, and it aids in the detection of patients who will need further evaluation. In order to identify families with LS, geneticists utilise family history-based criteria, mainly the Bethesda and Amsterdam II criteria (Table 1) for initial screening. The Amsterdam I criteria were specific for CRC but were modified to the Amsterdam II criteria to involve other extracolonic cancers. The Bethesda and modified Bethesda criteria were mainly developed to identify patients who required tumour testing for MSI. The Amsterdam II and Bethesda criteria are predominantly based on family history and clinical background and therefore carry a low sensitivity, which makes them insufficient as independent screening tools.

Further screening with tumour IHC is being used increasingly to identify women who should undergo germline molecular testing. Mutated MMR genes result in loss of expression of MMR proteins, and on IHC the loss of these proteins causes

**Table 1: Revised Amsterdam II criteria**

| Requirement                                                                 | Notes                                                                                                                                 |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| At least three relatives with HNPCC-related tumours (CRC, endometrial cancer, small bowel, ureter or renal pelvis) | One should be a first degree relative of the other two                                                                                  |
| At least two successive generations should be affected                    | At least one should be diagnosed before the age of 50 years                                                                          |
| Familial adenomatous polyposis should be excluded                         | Familial adenomatous polyposis should be excluded                                                                                     |
| Tumours should be verified by pathological examination                     | CRC = colorectal cancer; HNPCC = hereditary non-polyposis colorectal cancer                                                            |
loss of staining. A positive IHC result warrants germline testing. Therefore, IHC followed by targeted germline molecular testing offers the highest sensitivity for the diagnosis of LS.6

Making a definitive diagnosis of LS is therefore complex and very challenging in a resource-poor country like Zimbabwe. Considering her family history, when Mrs SB was diagnosed with CRC she should have been referred to a geneticist. Unfortunately, in Zimbabwe there are no geneticists in public or private sector hospitals. The counselling and screening of women with suspected hereditary cancers is left to surgeons who are not trained to undertake this task. Due to poor remuneration, this challenge will not be solved in the near future.

Another missed opportunity for Mrs SB was that colorectal surgeons at Parirenyatwa Hospital do not hold established MDT meetings and this case really bring to the fore why MDT meetings should be mandatory for all cancer patients. An MDT meeting might have resulted in an earlier referral to gynaecology oncology for screening for endometrial and ovarian cancers.10, 11 If her family was complete at the diagnosis of CRC, she would have benefited from a risk-reducing total hysterectomy and bilateral salpingo-oophorectomy. This has been shown to be cost-effective and beneficial in reducing gynaecological malignancies associated with LS.12

When Mrs SB was seen in the gynaecology oncology clinic, LS was strongly suspected based on her strong personal and family history. Unfortunately, even then, numerous hurdles were encountered including the lack of outpatient endometrial sampling devices, resulting in improvisation with an MVA kit to secure a diagnosis.

Frozen section and magnetic resonance imaging (MRI) scans are not available in all the public hospitals in Zimbabwe to triage women with endometrial cancer to detect the sub-group of women with low-risk disease who might not benefit from lymph node dissection. Lymph node dissection can lead to increased morbidity without oncological benefit in women with low-grade and superficial cancers.13 Due to high out-of-pocket expenses, Mrs SB was unable to have her lymph nodes assessed histopathologically, and if this had been known in advance, the procedure should not have been undertaken. Since IHC screening and germline molecular testing are unavailable in Zimbabwe, there is no capacity to confirm the LS diagnosis definitively. In her case, a presumptive diagnosis was reached after the Lancet Laboratory in South Africa agreed to do the test free of charge at the request of the gynaecologist oncologist managing her. Therefore, in Zimbabwean hospitals, the Amsterdam II criteria are used to make a presumptive diagnosis of LS and clinical decisions are based on this. Considering the low sensitivity, this is not ideal.

Other challenges in managing Mrs SB were the delay in her surgery due to the industrial action by healthcare workers at the public hospital, and the fact that there was no access for screening and long-term follow-up of her children due to high out-of-pocket expenses. Family counselling and screening is of paramount importance in the early detection and treatment of any LS-associated cancers, which tend to occur at younger ages in at-risk families.14

Conclusion
This case demonstrates the numerous challenges faced in the diagnosis and management of suspected LS-associated malignancies in Zimbabwe. High out-of-pocket expenses remain a significant barrier to health care access for women with gynaecological malignancies. The government needs to make screening and treatment of gynaecological malignancies free if all these problems are to be meaningfully addressed.

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