

**ORIGINAL ARTICLE**

# Multiple Primary Malignancies in Patients: Case Reports of Five Patients in Northern Zambia

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## ABSTRACT

Occurrences of multiple discrete synchronous or metachronous primary neoplasms in a single patient though reported are not a common occurrence.

In the last the last ten years five patients presented to Nchanga South Hospital in Chingola, Zambia with multiple discrete malignancies. The mean age of our patients was 43.6 years. The oldest was 56 years old and the youngest was 36 years old. Four of our patients were females.

Two patients had cancers of the colon followed by ovarian malignancy in one and a rectal malignancy in the other. Of the other patients, one had cancer of the cervix and later she developed None Hodgkin's lymphoma. Two had bilateral breast malignancies.

In two of our patients there was synchronous development of the tumours and in three there was Metachronous development

The risk factors in our patients were; receiving chemotherapy and/or radiotherapy and the presence of HIV.

## INTRODUCTION

The development of multiple primary tumors in a single patient is uncommon in our practice but has been

reported<sup>3</sup>. Some workers have found as many as five synchronous neoplasms in one patient which is acceptedly a rare event<sup>4</sup>. In most reports these cases include multiple discrete tumors within the same or contra lateral-paired organ. We present five cases of patients who developed multiple primary tumours synchronously and metachronously.

## CASE REPORTS

### The First patient

GM a 54 years old female was first seen in April 2009 with complaints of; pain on the left side of abdomen for one week but had the most sere pain the night before her admission. She had no fever and no diarrhea but vomited once.

She reported the pain to have come and gone for many years and that once, seven years previously, she had a similar severe attack. She also said she was prone to constipation. She had no other complaints and the review of her other systems did not reveal anything significant. There was history of secondary infertility as she had had two children only in her life. The third pregnancy ended in an ectopic pregnancy which was treated conservatively. She revealed that she had a laparoscopy and hysterosalpingiography when she was being investigated for secondary infertility. She was found to have a blocked right tube and a scarred left tube. The ovaries were normal.

**Key words:** Tumours, Primary, Metachronous, Synchronous

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Her daughter had primary infertility. Her mother had ten children and all her siblings were of normal fertility.

On examination she was found to be in good state of health.

The abdomen was soft and mildly tender. There were no masses and no organomegaly. She was given laxatives and sent home.

Five months later, she presented with severe colicky abdominal pain and history of not passing stool or flatus for two weeks. She had vomited several times on the day she presented.

The review of other systems did not yield anything significant.

On Examination this time the patient looked ill and was found to have intestinal obstruction.

The patient was consented for a laparotomy and at operation she was found to have a malignant stricture in the descending colon which, on histology, turned out to be a well differentiated adenocarcinoma of the at Duke's stage C<sub>1</sub>. All the other organs including her ovaries were inspected during Laparotomy and were found to be normal. She recovered well and was discharged from hospital on the 6<sup>th</sup> post operative day. One month later she was scanned by ultra sound and no abnormality was found. She was started on 5- Fluorouracil 500mg intravenously once a month and she received three cycles.

When she came for the fourth cycle, she complained of abdominal fullness and was found to have a large mass in the lower abdomen.

Ultra sound examination revealed bilateral Tubo-ovarian masses. X-ray of the abdomen indicated intestinal obstruction. The patient was admitted and booked for laparotomy.

On the 22<sup>nd</sup> of January 2010 she was operated upon for the second time. There were many adhesions in the abdomen but the significant finding was that both ovaries carried large tumours the left one was about 10cm x10cm in size and the right one was about 12cm x10cm. The uterus

appeared to have been invaded posteriorly. The appendix was entangled in the mass on the right side.

Both masses were excised; a subtotal hysterectomy and appendicectomy were also performed. There was one solitary mass on the Liver which at the time of surgery was deemed to be a secondary, but it was not certain whether this was a secondary from the first malignancy or from the ovarian tumours.

Then ovarian masses being almost of the same size it was assumed the tumours started spontaneously in each ovary as opposed to one being a secondary of the other. The histology report showed the tumours to be malignant mucinous cystadenocarcinomas. The uterus had Leiomyomata and was free of tumour and the appendix was normal. Breast examination revealed no lumps and no nipple discharge so, inspite of the absence of mammography, the breasts were assumed to be normal.

The HIV test in the patient was negative. The chest radiograph was normal

### **The second patient**

BMC a 36 year old female was a known HIV positive patient on HAART. In 2008 she was found to have ca. cervix and subsequently underwent radical hysterectomy in June 2008. She received both Chemotherapy and radiotherapy for her cancer during the course of 2009.

In January 2010 she presented to the surgical outpatient clinic with enlarged neck and axillae lymph nodes. These were biopsied and a diagnosis of Non-Hodgkin's lymphoma of the large cell variant was arrived at by histopathology. The patient went on to develop severe back pain and general bone pain. She was also found with an enlarged and irregular liver. X- Rays of the Lumber spine and chest did not show any bone metastases. The back and bone pain were thought to be resulting from bone marrow infiltration by the lymphoma. Ultra sound scan was done and it revealed lesions consistent with infiltration of the liver by the Lymphoma. She died shortly after starting her chemotherapy.

The conclusion was that this lady had developed a second primary tumour in the name of a large cell lymphoma in addition to the Cancer of the cervix she already had. We deduced that these tumours must have occurred metachronously. Both cancers in her were histologically proven.

### **The third patient**

AM was a male patient who was 36 years old. He first presented to hospital in December 2007 when he was 33 years old with history of abdominal pain, vomiting and constipation. Laparotomy was done and a malignant stricture was found along the transverse colon. The histology of the lesion reported a well differentiated adenocarcinoma of the transverse colon and was staged Duke's stage B. The patient recovered well after the surgery and underwent a six cycle course of 5-fluorouracil.

In May 2010 the patient presented to the hospital with a fistula in-ano and at fistulectomy, the surgeon found normal anal and rectal mucosae. There were no signs to indicate any rectal malignancy. Four months later the patient came back with complaints of pain in the perineum and passing small amounts of stool. The stool was blood stained. The patient was examined under anesthesia and found to have a large rectal tumour. The tumour was removed by abdominal perineal resection operation. The histology reported a well differentiated adenocarcinoma of the rectum and was staged Duke's B. It was believe this was a metachronous event.

The patient was tested for the HIV infection and he tested positive.

### **The Fourth Patient**

EC was a 56 year female who came in with the complaints of nipple discharge from both nipples, she also complained of having painless lumps in both breasts. On examination she was found to have breast masses in both breasts. The sizes were approximately 3x2 cm. They were hard in consistency and not tender. She had no palpable axillae nodes. Lumpectomies were done and the histology report showed Invasive Ductal

adenocarcinomas in both lumps. The patient received Chemotherapy and tamoxifen and was later referred to the cancer center for further management. It believed this was a synchronous event. She was not HIV positive

### **The Fifth patient**

CM was 36 years old when she presented to us with bilateral fungating ulcers in both breasts. The ulcers had started as itchy lesions of both breast nipples which had troubled her for about one year. The biopsy of both ulcers revealed invasive Ductal adenocarcinomas of the breasts. She had enlarged axillae nodes as well. The patient received chemotherapy and radiotherapy before mastectomy. She tested positive to the HIV infection.

### **Discussion**

The development of multiple malignancies in a single individual, which may be secondaries of a primary tumour somewhere in the body, is commonly reported.

However discrete synchronous or metachronous primary neoplasms in a single patient, though reported, are not a common occurrence.

In a study of 406 consecutive patients who were diagnosed with soft tissue sarcomas, Ukihide Tateishi<sup>1</sup> et al found that a total of 35 patients with soft tissue sarcomas (9%) had other primary malignancies. Of these patients, 15/ 35 (42.8%) had other preceding malignancies before the soft tissue sarcomas were diagnosed and 20/35(57.2%) had subsequent malignancies other than soft tissue sarcomas<sup>1</sup>. At the time of writing we had seen 213 cases of various malignancies passing through the surgical department over a period of ten years. All the three cases fit into Ukihide Tateishi's second category if we used carcinomas as the reference point in the case of Gastro intestinal malignancies, Moises Diamante and Harry Baconi reviewed a series of 2,508 patients with malignancies of the large intestines to determine the incidence of primary multiple neoplasms they found the incidence to be 9.1%. They noted that the colon was most frequently involved.<sup>5</sup> Our prevalence rate stands at 2.3% perhaps because our figures are still small.

Our first case was a 54 years old lady who presented with tumours of both ovaries synchronously five months after having surgery for a Duke's C<sub>1</sub> malignancy. Whereas we believe the colon cancer was a primary tumour which developed metachronously to the ovarian tumours, we can assume that the ovarian tumours were also primary lesions and not secondary from the colon because mucin producing cystadenocarcinomas can and do occur as primary ovarian cancers as described in pathology text books. At the time of diagnosis the two tumours were of the same size. The mucinous types of ovarian cancers are epithelial tumours and form 10% of ovarian cancers; of which 20% are bilateral, 10% of patients have evidence of ovarian or ovarian-breast cancer syndrome and the remainder are sporadic. Our patient did not have any breast pathology so she was in the sporadic group. In terms of pathogenesis it is due to mutations in BRCA1 in a small number of cancer families.

In terms of epidemiology, these are most common in women who are peri- or post-menopausal aged 45-70 years, women of low parity and women with gonadal dysgenesis<sup>10</sup>; our patient was post menopausal and of low parity.

Mucinous cystadenocarcinomas is clinically staged as: Stage I which confines to ovary (ies), Stage II confines to pelvis, Stage III has extension to abdominal cavity and Stage IV has distant metastases. Our patient had one solitary lesion on the dome of the right lobe of liver. So she was stage IV. Most women present at Stage III or IV spread across serosal surfaces and to lymph nodes are common<sup>10</sup>. Our patient did not have much in terms of enlarged lymph nodes in the abdomen.

Our Second case was that of an adenocarcinoma of the cervix which was later followed by the development of NonHodgkin's Lymphoma.

Our third case was a patient with a well differentiated adenocarcinoma of the transverse colon who three years later presented with a well differentiated adenocarcinoma of the rectum.

The fourth and fifth patients presented with bilateral ductal carcinomas of the breasts and in both these two

cases, the malignancies appeared to have started at the same time hence were synchronous lesions.

A Japanese study identified the risk factors for the development of multiple primary malignancies to be age of the patient at presentation and presence of certain malignancies like myxofibrosarcomas<sup>1</sup>. It is also known that Thymoma patients appear to have an inherent predisposition towards developing additional neoplasms other than the thymoma<sup>3</sup>. Moises Diamante and Harry Baconi in their review noted that the colon cancer was most frequently involved as a risk factor<sup>5</sup>. Our first patient had the risk factor of having a colon malignancy and she was 54 years old. Our fourth patient was 56 years old. However three of our patients were around 36 years of age and outside the age group at highest risk.

Other studies have demonstrated that family history of cancer and genetic predisposition to cancer may be associated with a risk of multiple malignancies. For example correlation between the incidence of multiple malignancy and familial aggregation has been demonstrated in Li-Fraumeni syndrome<sup>2</sup>. There was no history of cancer in any of our patient's families.

The other causes may be oncogenic viruses such as HPV and HTLV1. DNA damaging toxins and exposure to carcinogens are other causes<sup>4</sup>. Our first patient tested negative to the HIV virus. Two of our patients, were HIV positive. Despite being on HAART and seemingly responding well, one our patients went on to develop another Primary tumour.

Drugs used in cancer management have also been implicated in the development of other primary cancers synchronously or metachronously. One such drug is Tamoxifen which is associated with endometrial cancer after long term use<sup>4</sup>. We quote Fletcher et al who wrote "The development of a second primary cancer after treatment of the first with radiotherapy or chemotherapy is well documented. This is often seen with hematological malignancies in childhood where other malignancies, usually hematologic follow, when there is good five year survival<sup>4</sup>." Two of our patients received 5 Fluorouracil.

Our first patient received it for three months only our third patient got the full six months cycle of the drug and our second and fifth patients had received both radiotherapy and Chemotherapy for their cancer of the cervix and breasts respectively.

There is also a possibility that the ovarian tumours in our patient were secondary lesions to the Ovaries arising synchronously from the Colon cancer that was resected five months previously even if only 5% of ovarian cancers are as a result of Metastasis. The most common sites from which they spread are the colon (52%), breast (17%), stomach (10%), and pancreas (5%).

Ovarian metastasis from colon cancer is however reported by some authors to be relatively rare and has a poor prognosis; Fujita Shigeo et al reported two cases of ovarian metastasis from colon cancer. One was found after curative resection of colon cancer, and the other synchronously with primary colon cancer at the time of initial diagnosis<sup>6</sup>.

The histological types of the lesions from colon cancer as a primary site to the ovary according to Choi et al were tubular adenocarcinoma (61.3 %,) and mucinous adenocarcinoma<sup>7</sup>. It can be hypothesized that the mucinous cystadenocarcinoma we saw in our patient was a poorly differentiated form of the well differentiated colon cancer we initially found. The case of our second patient is very clear that this was a metachronous primary lesion.

Sakakura et al describes the case of a 34-year-old premenopausal woman in whom bilateral huge ovarian metastases were found 2 months after initial surgery for sigmoid colon cancer. Both ovaries had been intact at the time of sigmoidectomy, this was much like our first patient but later, their patient complained of persistent vaginal bleeding, and large bilateral metastases were detected in both ovaries<sup>8</sup>. In this case they demonstrate that metastatic colon cancer to the ovary may occur even in young women and that perhaps one should consider doing prophylactic oophorectomy in these cases.

These tumours tend to be huge by the time they present<sup>5,8,9</sup> because the symptoms at presentation tend to be vague. When the colonic primary and the ovarian secondary occur synchronously, the ovarian metastases are significantly larger than the primary colon tumors at exploration<sup>9</sup> The tumours we found in our patient were huge.

## CONCLUSION

We conclude that despite there being a possibility that these tumours in our first patient were secondary malignancies from the colon cancer we resected five months earlier, the most likely scenario is that these were primary tumours that arose synchronously in both ovaries. We were disappointed that the tumours were so large when we explored the patient and suggest that in post menopausal patients with colon cancer a prophylactic oophorectomy should be considered because of the possibility of development of primary or metastatic cancer in the ovaries.

In our third patient we conclude that these were metachronous tumours of the large bowel despite the fact that there were no other lesions of the large bowel at colonoscopy of the remaining bowel.

In the case of our second and fifth patients we point out that HIV positive patients who have one malignancy treated should be watched for the development of other primary tumours irrespective of how well they are doing on HAART.

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