Journal of Advances in Medicine and Medical Research

32(9): 1-9, 2020; Article no.JAMMR.58275
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Mucinous Adenocarcinoma of the Colon in Uganda: A Case Report and Literature Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i930475
Editor(s):
(1) Prof. Dr. Emin Umit Bagriacik, Gazi University, Turkey.
(2) Chan-Min Liu, Xuzhou Normal University, PR China.
Reviewers:
(1) Summyia Farooq, Government Medical College Srinagar, India.
(2) Sathesh Kumar Sukumaran, Vels Institute of Science, India.
(3) Arslan Hassan, Bahauddin Zakariya University, Pakistan.
Complete Peer review History: http://www.sdiarticle4.com/review-history/58275

Case Study

Received 08 April 2020
Accepted 14 June 2020
Published 19 June 2020

ABSTRACT

Introduction: In Uganda, the Kampala Cancer Registry has reported a steady increase in the incidence of colorectal carcinoma(CRC) over the last few decades. The author reports a case of a 25 year old gentleman presenting with bowel obstruction and found to have mucinous adenocarcinoma of the colon. This is followed by a literature review of the clinical and pathological characteristics of young age sporadic colorectal carcinoma (YSCC) and hereditary nonpolyposis colorectal carcinoma (HNPCC).

Presentation of Case: This patient presented with a family history of colorectal carcinoma (CRC) and with bowel obstruction. An emergency laparotomy involving a right hemicolectomy was carried out. The postoperative course of this patient was uneventful.

Discussion: The typical histological features of mucinous adenocarcinoma of the colon were seen on the resected colon specimen. In addition this study reviews the literature regarding the clinical presentation, pathological characteristics, histology and prognosis of mucinous and medullary carcinoma of the colon.

Conclusions: Mucinous adenocarcinoma happens to be the most common histological type of colorectal carcinoma in young adults. In Uganda, low risk young patients with symptoms should be screened for colorectal lesions. A high index of suspicion should therefore be taken in the diagnosis of colorectal malignancy in these patients.

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Keywords: CRC: colorectal carcinoma; YSCC: young age sporadic colorectal carcinoma; HNPCC: hereditary non polyposis colorectal carcinoma; MSI: microsatellite instability.

1. INTRODUCTION

Colorectal cancer is the fourth leading cause of cancer death in the world [1,2]. It is the third most commonly diagnosed malignancy in the world and is responsible for 1.4 million new cases and approximately 700,000 deaths in the year 2012 [2]. CRC is the second most common cancer in women wordwide (614,000 cases; 9.2% of the total) and the third most common cancer in men (746,000 cases; 10% of the total) [2]. In Africa colorectal carcinoma is a rare disease and it currently represents 2-6% of all malignant tumors [3]. In Sub-Saharan Africa there is a steady increase in the incidence of colorectal adenocarcinoma especially in urban areas [2,3]. The crude incidence of CRC in sub-saharan Africa is 3.69/100,000 for women and 4.38/100,000 for men (overall 4.04/100,000) [2,3].

In Uganda, the Kampala Cancer Registry in the Department of Pathology, School of Biomedical Sciences, College of Health Sciences, Makerere University in Uganda has shown that colorectal carcinoma has a low incidence however there are increases occurring especially among women [4]. Table 1 depicts the steady increase in the incidence of CRC in the last decades in Uganda from 3.0 to 8.8 per 100,000 population over the period 1960-2012 [5,6]. This steady increased incidence is being seen especially among women [6]. The age standardised incidence rate has increased from 5.2 per 100,000 population for the year period 1991-1995 to 9.0 per 100,000 population for the year period 2006-2010 in females [6]. Whilst the age standardised rate has since remained oscillating around 7.8 per 100,000 population in males for the years 1991-2010 [6]. During the period 1991-2006 the average percentage (%) change in age-standardised incidence rate in colon cancers was 6.3% in females and 0.5% in males [2,6].

Approximately 60% of colorectal carcinomas are sporadic and have no family history. These patients have no inherited gene mutation causing CRC [7]. 30% of colorectal carcinomas are familial and these patients tend to have at least one first degree relative with an adenoma or CRC. These patients have no specific germline mutation [7]. 10% of colorectal carcinomas are hereditary and these cancers result from germline mutations of specific mutations [7,8]. Prevalent hereditary colorectal cancer syndromes include familial adenomatous polyposis (FAP) syndromes and hereditary nonpolyposis colorectal cancer (HNPCC) syndrome also known as Lynch syndrome. The author reports on a case of a 25 year old gentleman who was found to have a mucinous adenocarcinoma of the caecum extending into the ascending colon without any risk factors. This is followed by a literature review of the clinical and pathological characteristics of young age sporadic colorectal carcinoma (YSCC) and hereditary nonpolyposis colorectal carcinoma (HNPCC).

2. CASE REPORT

A 25 year old gentleman from Masaka, Uganda, presented to our hospital with a five month history of right sided abdominal discomfort. He had progressive weight loss but did not have any vomiting or symptoms of altered bowel habit apart from a failure to pass stool for 5 days. An examination of other systems and his medical and surgical history was unremarkable. In his family history he reported his mother and other brother having passed away due to advanced colon adenocarcinoma. His older brother was only 26 years of age when he was diagnosed with advanced colon adenocarcinoma.

Table 1. Incidence rates of colon carcinoma quoted are age standardised incidence rates (per 100,000) over four time periods

Year	1960	1991-1995	2006-2010	2012
Incidence rate of colon carcinoma	3.0	-	-	8.8
Incidence rate of colon carcinoma (females)	-	5.2	9.0	-
Incidence rate of colon carcinoma (males)	-	7.8	7.8	-

On examination he was cachectic and his body mass index was 21. He was pale and had no lymphadenopathy. He had no stigmata of liver disease, lymphoma or human immunodeficiency virus (HIV). An abdominal examination revealed fullness in the right iliac fossa and mild abdominal distention whilst the rectal examination was unremarkable.

A chest X-ray was normal however a plain abdominal X-ray revealed signs of small bowel obstruction. The results of the haematological and serum biochemical tests were normal. The patient was resuscitated with fluids and an NG tube and catheter placed. He was consented to undergo an emergency laparotomy following resuscitation. At laparotomy evidence of a caecal tumour extending in to the ascending colon was found. There was evidence of mild ascites with normal liver texture. A right hemicolectomy was carried out and an ileotransverse anastomosis was performed with good end result. The patient made an uneventful post-operative recovery. Histopathology of the resected colon specimen confirmed a mucinous adenocarcinoma of the colon.

3. DISCUSSION

3.1 Presentation of Mucinous and Medullary Carcinoma of the Colon

10-15% of all colorectal carcinomas tend to be mucinous adenocarcinomas and are a distinct subgroup of adenocarcinoma. Mucinous adenocarcinomas only constitute 5% of adults with colorectal carcinoma whilst 28% of these lesions are found in younger patients [9,10].

Medullary carcinoma of the colon represented 5-8 cases for every 10,000 colon cancers diagnosed between 1973 and 2006 according to the Surveillance Epidemiology and End Results (SEER) database [9]. The mean age at diagnosis is 69.3 +/- 12.5 years with men being diagnosed earlier than women, 64.3 +/-13.3 years versus 72.1+/-11.2 years respectively [10]. There is a significant female preponderance with a male:female ratio of 2:1 [10].

In East Africa a significant proportion of patients are young with a median age at diagnosis of 41-59 [11-13]. Between 19% to 38% of patients younger than 40 years of age present with CRC [13]. This is in contrast to only 1.9% of patients in the USA who are younger than 40 years and present with CRC [13]. Among African-American patients, early-onset CRC has also been described [11]. In Uganda, Dixjhoorn, found that colorectal carcinoma is diagnosed at a median age of 55 years, 30.6% of CRC patients are under 50 years of age, 6.9% of CRC patients are under 30 years of age and 69.4% of CRC patients were either 50 years or above [13].

Medullary carcinoma tends to be commonly found in the proximal colon and generally presents in older females at an earlier stage [9]. These tumours tend to present in the right colon, mainly the caecum as large bulky masses. Invasion of the colonic lumen by the tumour as a sessile polyp with central ulceration is the classical presentation. The majority of these tumours extend extra-luminally with infiltration of the pericolic soft tissues. In a study by Thirunevukarasu P et al the median tumour size was found to be 7 cm consistent with T3 tumours without nodal involvement and therefore presenting as a stage IIA. Some studies have shown evidence of local invasion and regional lymph node metastasis however liver metastases is rare [9]. Distant metastases at the time of diagnosis have been described in only 10% of patients [9,14,15].

A higher frequency of poor differentiation, loss of MMR expression, increased MUC2 expression and advanced stage is seen in mucinous adenocarcinoma compared to non-mucinous adenocarcinoma. However compared to medullary carcinoma the tumour location of mucinous carcinoma in YSCC is mainly in the left colon and rectum whilst in HNPCC mucinous carcinoma is predominantly in the right colon [14,15].

3.2 Pathways of Tumorigenesis Seen in Mucinous Carcinoma and Medullary Carcinoma of the Colon

An increased risk of CRC is seen in young patients with inflammatory bowel disease, polyposis syndromes of the gastrointestinal tract and hereditary non-polyposis colon carcinoma (HNPCC). Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is defined as an autosomal dominant disease caused by a germ line mutation of mismatch repair genes (MMR- genes) and leads to early onset colorectal carcinoma [16]. Underlying mutations that have been identified include MLH1, MSH2, MSH6, PSM1 and PMS2 genes [16]. 90% of all disease causing mutations are caused by MLH1 and MLH2 genes [17]. The most commonly used

diagnostic criteria for HNPCC include the Amsterdam criteria which include (1) Three or more family members with histologically verified colorectal cancer (2) one member will be a first degree relative of the other two (3) one case should be diagnosed before the age of 50 years (4) over two or more successive generations [18].

This patient reported by the author clearly shows that the Amsterdam criteria are fulfilled and therefore genetic testing for MSI is required to establish the molecular subtype and therefore whether this patient really has HNPCC. Germline MMR gene mutations are seen in most patients with clinically diagnosed HNPCC [19]. Identification of these patients without a family history and with germline MMR gene mutations is very important [19]. However MMR gene mutations are unlikely to occur in most young colorectal cancer patients without a family history of HNPCC [19]. Young age sporadic colorectal carcinoma and hereditary non-polyposis colorectal carcinoma tend to arise from a mutator phenotype genetic pathway of colorectal carcinogenesis [20]. However hypermethylation of the MMR gene MLH1 instead of gene mutation itself may be responsible for young age sporadic colorectal carcinoma [20]. Sporadic colorectal carcinomas with a high level of MSI are caused by epigenetic silencing of the promotor regions of the MMR genes, mainly MLH1 by CpG island hypermethylation [21]. 3-5% of all CRCs are associated with an MMR gene defect which results in the absence of MMR protein expression. 15-20% of all CRCs are due to a somatic mutation due to hypermethylation of the MLH1 promotor. MSI tumors tend to be poorly differentiated, of mucinous or signet ring histological type and located in the proximal colon, contain tumor infiltrating lymphocytes and Crohn's like reaction [7,22]. The histologic subtypes of colorectal carcinomas which are more commonly observed in MSI tumours include medullary carcinomas, mucinous carcinomas and signet ring carcinomas [7,22]. MSI tumors have a better prognosis when compared to MSS [23].

MSI has been associated with MMR gene alterations and account for 15-20% of sporadic carcinomas and 85% of hereditary colorectal carcinomas [23]. MMR germline mutation is associated with a 70-80% lifetime risk of developing colorectal carcinoma compared to 5-6% of the general population [16]. Tumors with an MMR gene defect will show an absence of MMR protein expression, which may be secondary to either a germline mutation (3-5% of all CRCs) or a somatic mutation usually hypermethylation of MLH1 promotor (15-20% of all CRCs) [16]. BRAF mutation is evaluated in MLH-1 protein negative expression and it is often present when the MLH-1 promotor is methylated [16]. Immunohistochemistry is a valid tool to identify patients at risk for HNPCC and patients with sporadic microsatellite unstable CRC [16,17].

In human colorectal carcinoma aberrant hypermethylation of DNA results in the silencing of tumor suppressor genes [24,25]. Colorectal carcinomas with a high degree of methylation (CIMP) tend to develop from the sessile serrated adenoma as their precursor lesion [7]. Traditional serrated adenomas also known as classic adenomas result in colorectal carcinoma withy low methylation [7]. CIMP tumors tend to be more common in proximal tumors [26]. CIMP+ tumors are also associated with a higher tumor grade and stage, mucinous histological type, KRAS mutation, wild type p53 and tumor infiltrating lymphocytes [27,28]. Male sex and K-ras mutations has been associated with the CIMP negative subgroup [29].

Inappropriate silencing of gene expression is found in the CpG islands which are aberrantly hypermethylated [29]. CIMP are a subgroup of colorectal carcinomas which are methylated at promotor regions (CpG islands) and hence silence the genes promoting tumorigenesis. On the other hand there are scattered CpG dinucleotides which are methylated in normal cells and unmethylated in cancer [30]. Promotor hypermethylation is a tumorigenic pathway which is characterised by epigenetic rather than genetic inactivation of tumor suppressor genes [31].

Higher frequencies of poor differentiation, loss of MMR expression, increased MUC2 expression and advanced stage are seen in mucinous adenocarcinoma compared to non-mucinous adenocarcinoma [32]. A similar proportion of advanced tumour stage between mucinous and non-mucinous adenocarcinoma is seen in young sporadic colorectal carcinoma [32]. The tumour locations of mucinous adenocarcinomas are different between young sporadic colorectal carcinoma which are predominantly in the left colon and rectum whilst hereditary non polyposis colorectal carcinoma is predominantly located in the right colon [32].

3.3 Histology and Diagnosis of Mucinous Carcinoma and Medullary Carcinoma of the Colon

In mucinous carcinoma (Fig. 3), the tumour may infiltrate the mucosa and is composed of lakes of mucin. In signet ring variants the tumour cells have abundant cytoplasm with hyperchromatic, pleomorphic and densely stained nuclei which when pushed to the peripheral parts of the tumour cells have an appearance of signet rings. The tumour may be surrounded by granulation tissue which consists of fibrosis and sparse lymphocytes [33].

Medullary carcinoma is characterised by a solid growth pattern with an undifferentiated or poorly differentiated predominantly sheets of uniform type malignant cells associated with intraepithelial lymphocyte infiltrate and non-glandular pattern [33]. This histological type of adenocarcinoma (Figs. 1, 2 & 4)) can be differentiated from undifferentiated and poorly differentiated colon adenocarcinomas by loss of staining for MLH1, intestinal transcription factor CDX-2 and microsatellite instability [14,33]. Compared to other poorly differentiated colonic adenocarcinomas immunohistochemical staining has demonstrated a strongly positive calretinin [33]. Endocrine markers are usually negative and prior to initial treatment CEA levels may be high [33].

The diagnosis of medullary carcinoma of the colon is made by elevated tumour markers, histologic confirmation of the diagnosis and clinical features of a lower gastrointestinal tumour [15,33]. Medullary carcinoma of the colon has similar histologic features to neuroendocrine tumours and stains positive for TFF-2, MUC-1 and MUC-2 [33]. Colonic medullary carcinoma and undifferentiated adenocarcinoma are difficult tumours to differentiate by microscopy alone. Calretinin staining, CDX-2 staining and loss of MLH-1 can be found in medullary carcinoma but not in undifferentiated carcinoma. One study showed the microsatellite instability and stabilisation of p53 was limited to medullary type poorly differentiated adenocarcinoma [33].

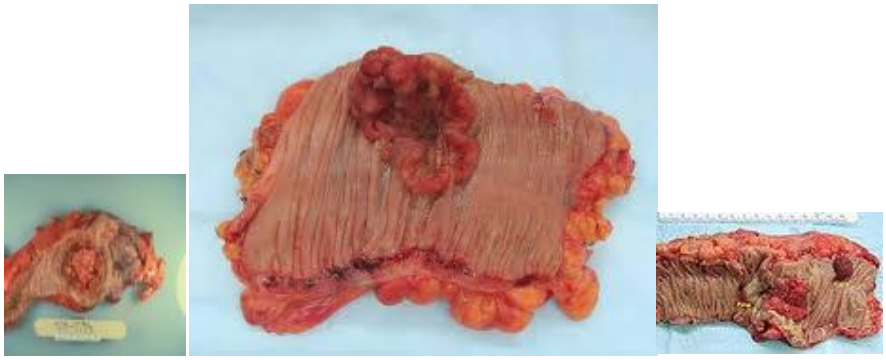

Fig. 1. Mucinous adenocarcinoma of the colon presenting as a polypoid single mass however may be ulcerated. If the muscularis propria is involved it may cause serosal puckering. Exophytic and polypoid lesions are characteristic of the right colon whilst annular encircling lesions are located in the left colon

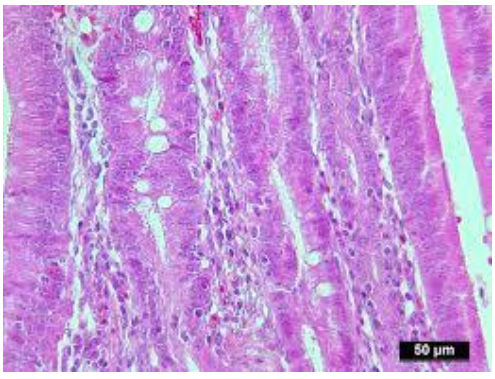

Fig. 2. Histology showing human adenocarcinoma of the colon

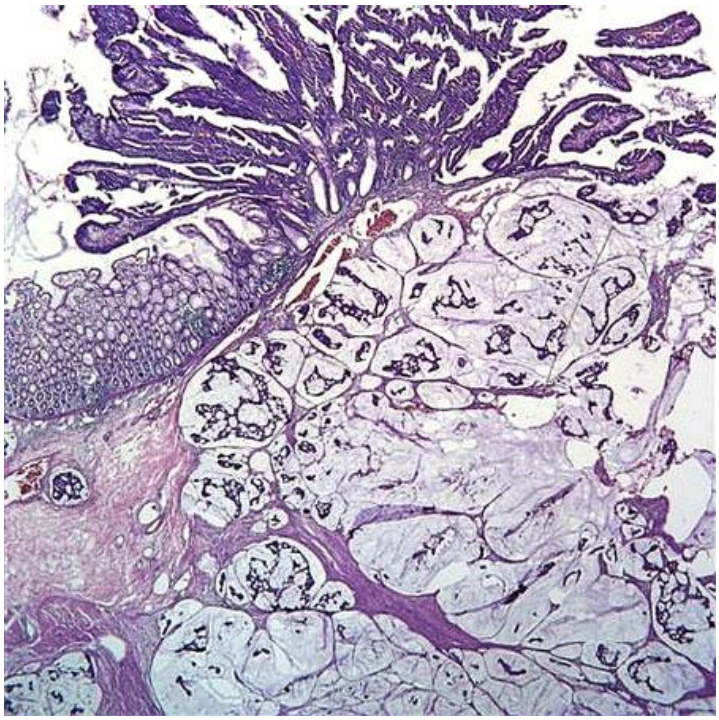

Fig. 3. Histology showing HE-stained mucinous adenocarcinoma of the colon. Mucinous adenocarcinoma consists of strips of tumour cells floating in large extracellular mucin lakes and comprising at least half of tumour mass. In less than half of the tumour signet ring cells with intracellular mucin may also be present

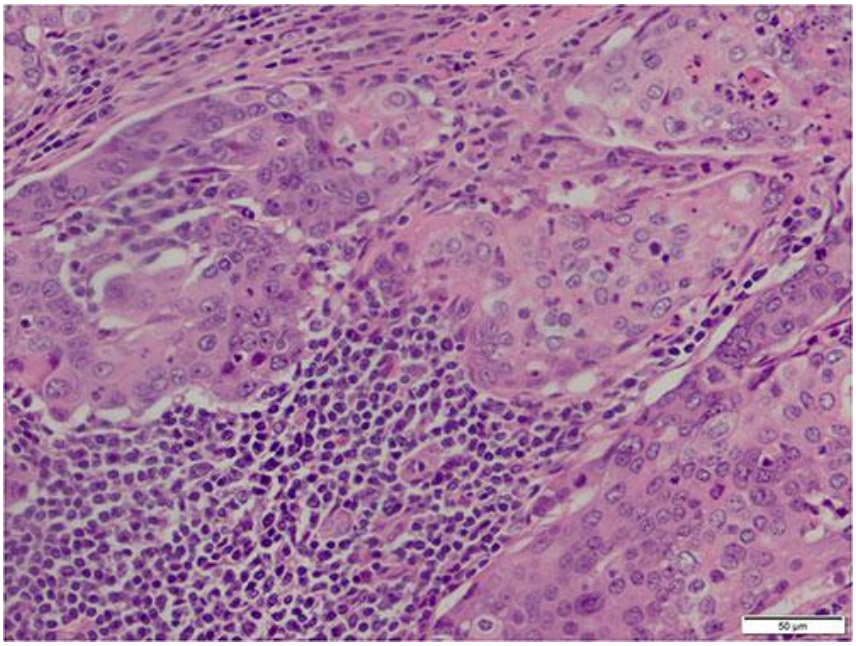

Fig. 4. Histology ofmedullary carcinoma of colon showing solid sheets, lacking in any gland formation, uniform small to medium sized nuclei, prominent nucleoli and nests of cells with prominent lymphocytic infiltrate

3.4 Prognosis of Patients with Mucinous and Medullary Carcinoma of the Colon

Studies from developed countries have compared stage for stagesurvival and found that young patients with mucinous histology having Duke's stage A or B tumours have better survival than elderly patients that have a similar stage CRC. However for histologically similar patients with Duke's C or D CRC then young patients do the same or worse than elderly patients with similar stage CRC. The treatment of CRC in young patients is the same as in elderly patients. A poor outcome among young CRC patients has been seen in a large cohort study [34]. This was due to the predominance of advanced stage CRC, incomplete resection, mucinous histology and the proportion of signet ring cells [34].

A relatively favourable prognosis is associated with medullary carcinomas compared to undifferentiated and poorly differentiated adenocarcinomas of the colon. Thirunavukarasu et al showed that the overall survival for medullary carcinoma was better at 92.7% at 1-year and 73.8% at 2 years compared to 70.5% and 58.4% for the poorly differentiated colon adenocarcinoma [9].

The patient presented in this case report had a right hemicolectomy for a caecal tumour proven to be mucinous carcinoma and tolerated chemotherapy with capecitabine and oxaliplatin well. However further studies are needed to determinethe prognostic factors and survival associated with the mucinous tumour subtype in our community due to the paucity of data in Uganda and the East African region.

4. CONCLUSIONS

In young adults in East Africa, colorectal carcinoma is occurring with increasing frequency. In MSI tumours the common histological subtypes of CRC include mucinous and medullary carcinomas. Mucinous adenocarcinoma happens to be the most common histological sub-type of CRC in young adults. Whilst another well-recognised sub-type of colon cancers is medullary carcinoma defined by microscopic and immunohistochemical characteristics. The overall prognosis is favourable compared to undifferentiated and poorly differentiated adenocarcinomas. Few studies look in to the different treatment strategies and their response. The improved survival seen with medullary carcinoma may be due to a low incidence of metastases at diagnosis. With more cases of mucinous carcinoma and medullary carcinoma of the colon being seen in Uganda the response to treatment as well as the prognostic factors of these histological sub types need to be determined.

The patient presented had a delayed diagnosis as the patient presented late with large bowel obstruction. However, most patients with colorectal carcinoma in Uganda and the rest of East Africa tend to present with late stage CRC hence resulting in a poor prognosis. In low risk young patients any change in bowel habit, rectal bleeding or unexplained abdominal pain should be screened for colorectal lesions. Therefore this case highlights the importance of screening young patients with symptoms of CRC without any risk factors. In young Ugandan patients a high index of suspicion should be taken in the diagnosis of colorectal malignancy and based on the patient's age, colorectal malignancy should no longer be excluded from consideration of this diagnosis.

CONSENT

The author declares that written informed consent was obtained from the patient for publication of this case report.

ETHICAL APPROVAL

This case report and literature review was partly taken from the PhD proposal of the author which was approved by the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda and Uganda National Council for Science and Technology (UNCST) and both approvals are preserved by the author.

ACKNOWLEDGEMENTS

The author declares that this case report and literature review was partly taken from his approved PhD proposal. The author wishes to express his sincere gratitude to Professor Michael Odida and Professor Henry Wabinga for their supervisory contribution to his PhD proposal.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/58275