ISSN: 2160-8792 Volume 12, Number 11, November 2022

Scientific Research Publishing

Open Journal of Obstetrics and Gynecology

ISSN: 2160-8792

https://www.scirp.org/journal/ojog

Journal Editorial Board

ISSN 2160-8792 (Print) ISSN 2160-8806 (Online)
https://www.scirp.org/journal/ojog

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Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 317-346
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Table of Contents

Volume 12 Number 11 November 2022

Open Journal of Gastroenterology (OJGas)
Journal Information

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Open Journal of Gastroenterology, 2022, 12, 317-323
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Epidemiological, Clinical, Paraclinical, Etiological and Therapeutic Aspects of Liver Cirrhosis in the Hepato-Gastroenterology Department of the Hospital Aristide Le Dantec in Dakar

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How to cite this paper: Bassène, M.L., Diallo, S., Fall, M.P., Thioubou, M.A., Sidibé, T., Cissé, C. and Gueye, M.N. (2022) Epidemiological, Clinical, Paraclinical, Etiological and Therapeutic Aspects of Liver Cirrhosis in the Hepato-Gastroenterology Department of the Hospital Aristide Le Dantec in Dakar. *Open Journal of Gastroenterology*, **12**, 317-323.
https://doi.org/10.4236/ojgas.2022.1211032

Received: October 1, 2022
Accepted: October 30, 2022
Published: November 2, 2022

Abstract

Introduction: Liver cirrhosis is a global public health issue. Our aim was to determine the epidemiological, clinical, paraclinical and therapeutic aspects of liver cirrhosis in the hepato-gastroenterology department of the hospital Aristide Le Dantec in Dakar. **Patients and Methods:** We conducted a retrospective study with a descriptive focus covering the period from January 1st, 2010 to December 31, 2020. We included the medical records of patients which presented body of clinical and paraclinical arguments which supported the diagnosis of cirrhosis. The data collected were related to age, gender, clinical, paraclinical, therapeutic and prognosis aspects of cirrhosis and were analyzed with the software Sphinx Plus. **Results:** Prevalence of cirrhosis was 6.2%. Sex ratio was 2.1%. The average age was 38 years. Asthenia (60.9%), altered performance status (60.1%), abdominal pain (37.2%), gastrointestinal bleeding (29.6%) and abdominal swelling (27.8%) were the most common motives of consultation. Physical examination revealed primarily portal hypertension (74.9%), liver failure (2.4%), hepatomegaly (28.2%) and anemia (13.7%). Viral hepatitis B was the most common etiology (81.9%). Abdominal screening (ultrasound/CT scan) showed hepatomegaly (80.6%), liver dysmorphia (87.7%), portal hypertension signs (85.3%) and portal vein thrombosis (18.2%). 55.1% Patients were classified as Child Pugh A, 33.8% were Child Pugh B and 11.1% were Child Pugh C. Tenofovir Disoproxil Fumarate (TDF) was prescribed to all patients affected by hepatitis B virus only. Evolution was characterized by

clinical improvement and prognosis reclassification. **Conclusion:** Liver cirrhosis is a frequent pathology in the hepato-gastroenterology department of the hospital Aristide Le Dantec in Dakar. It affects young male adult. Hepatitis B virus is the leading cause. TDF is an effective treatment.

Keywords

Cirrhosis, Viral Hepatitis B, Portal Hypertension, Liver Failure, Hepatomegaly

1. Introduction

Liver cirrhosis is a global public health issue. It results from, among other factors, chronic hepatic inflammation caused by various pathologies, leading to the hepatic tissue replacement with fibrotic tissue and progressive hepatic dysfunction [1] [2].

Cirrhosis prevalence and incidence are not well-known. It is estimated that one out of three cirrhosis, goes undetected due to the clinical latency which characterizes the disease. More often, it appears at a stage of complications that can be life-threatening with a very high morbidity/mortality rate [3] [4].

Etiological treatment plays a crucial role in the management as it can improve the prognosis.

In Senegal, few studies have been conducted on liver cirrhosis. To contribute to a better understanding of the pathology, which etiologies vary according to geographical regions, we have conducted a retrospective study aimed at describing the epidemiological, clinical, paraclinical, etiological and therapeutic aspects of cirrhosis in the hepato-gastroenterology department of the hospital Aristide Le Dantec in Dakar.

2. Patients and Methods

It was a retrospective study with a descriptive focus covering the period from January 1st, 2010 to December 31st 2020 in the hepato-gastroenterology department of the hospital Aristide Le Dantec in Dakar. Our study population was composed of hospitalized and/or ambulatory patients.

We included patient medical records which presented body of clinical and paraclinical arguments which supported the diagnosis of cirrhosis. Patients presented with one or more of the following signs:

- Clinical signs: shrunken liver, hepatomegaly, portal hypertension signs (collateral venous circulation, splenomegaly, ascites), liver failure (oedema of the lower limbs, jaundice, spider nevi, palmar erythema, digital clubbing, asterixis, fetor hepaticus, gynecomastia, hepatic encephalopathy).
- Biological signs: decreased prothrombin time, thrombocytopenia, hypoalbuminemia.
- Radiological signs: dysmorphic liver, with irregular contours, heterogenous liver parenchyma, dilated portal vein, splenomegaly, ascites, portocaval shunts.

- Endoscopic signs: gastroesophageal varices, hypertensive gastropathy.

The medical records of patients which did not contain enough diagnosis arguments in favor of cirrhosis, were not included.

The data collected in patients' records were related to age, gender, clinical (cirrhosis signs and associated signs), paraclinical (biological, radiological and endoscopic signs), therapeutic and prognosis aspects (Child-Pugh classification and cirrhosis complications) of cirrhosis and were analyzed using the software Sphinx Plus.

3. Results

We included 486 patients. Cirrhosis prevalence was 6.2%. There were 332 (68.3%) men representing a sex ratio of 2.1. Average age was 38 years with extremes of 15 and 92 years, and 79% of patients were under 50 (Figure 1).

Asthenia (60.9%) altered performance status (60.1%), abdominal pain (37.2%), gastrointestinal bleeding (29.6%) and abdominal swelling (27.8%) were the most common presenting complaint (Table 1). Average time to consultation was 6.2

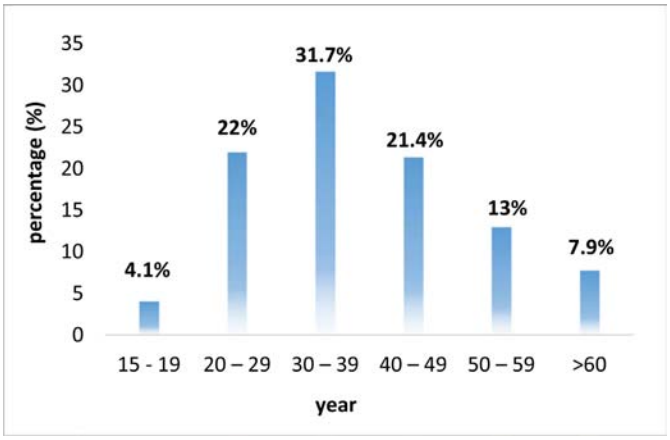

Figure 1. Distribution of patients by age.

Table 1. Distribution of patients by motives of consultation.

Motives of consultation	Cases number	Frequency (%)
Asthenia	296	60.9
Altered performance status	392	60.1
Abdominal pain	171	37.2
Gastrointestinal bleeding	154	29.6
Abdominal swelling	135	27.8
Pruritis	130	26. 7
Headache	63	13.6
Dyspnea	21	4.8
Constipation	19	3.9
Hepatic encephalopathy	2	0.4

weeks. Chronic HBS Ag carriage was found in 7 patients (1.4%). Familial medical history of hepatocellular carcinoma and chronic hepatitis B infection were respectively found in 25 (5%) and 20 (4%) patients.

Chronic tobacco consumption was present in 5.7% of cases. Alcohol consumption was signaled in 2.3% of cases; however, it was not quantified.

Interrogatory of patients revealed the used of oral phytotherapy in 13.7% of cases. Physical examination showed primarily portal hypertension signs (74.9%), liver failure (2.4%), hepatomegaly (28.2%) and anemia (13.7%) (Table 2).

Decompensation was marked by ascites in 154 patients (31.7%). The ascitic fluid was yellow citrine in 74.8% of cases, serohematic in 5.9% of cases, hazy in 15.5% of cases, chylous in 3.8% of cases. Spontaneous bacterial peritonitis was noted in 18 patients (3.7%).

Biological exams revealed elevated transaminases in 87.7% of cases, cholestasis in 59.2% of cases and liver failure in 61.3% of cases. Causes of cirrhosis was hepatitis B infection (81.9%). A coinfection with hepatitis C was present in 5 patients (1%), hepatitis D virus in 27 patients (5.6%) and HIV in 2 patients (0.4%)

Abdominal screening (ultrasound/CT scan) showed hepatomegaly (80.6%), liver dysmorphia (87.7%), portal hypertension signs (85.3%) and portal vein thrombosis (18.2%).

It highlighted typical image of hepatocellular carcinoma (HCC) which is arterial enhancement and washout on portal phase in 28.4% of cases. Upper endoscopy showed esophageal varices in 89.2% of patients and gastric varices in 12%.

Patients were classified as Child Pugh A in 55.1% of cases, Child Pugh B in 33.8% and 11.1% were Child Pugh C.

Table 2. Distribution of patients by physical examination signs.

	Signs	Cases number	Frequency (%)
	Hepatomegaly	134	28.2
	Shrunken liver	12	2.5
Liver Failure	Hepatic encephalopathy	7	1.4
	Digital clubbing	2	0.4
	Palmar erythema	1	0.2
	Fetor hepaticus	1	0.2
	Gynecomastia	1	0.2
Portal hypertension	CVC	37	7.6
	Ascites	154	31.7
	Splenomegaly	178	35.6
Cholestasis	Scratch induced lesions	2	0.4
	Anemia	64	13.7

CVC: collateral venous circulation.

Tenofovir Disoproxil Fumarate (TDF) was prescribed to all patients who were affected with hepatitis B virus only associated with a symptomatic treatment. Average follow-up time was 23 months [1 - 52 months]. Evolution was characterized by clinical improvement and prognosis reclassification. Patients who were classified Child-Pugh B were reclassified as Child A in 28.2% of cases, and those who were classified as Child-Pugh C were classified as Child B in 16.4% of cases.

We noted 36 cases of death (7.4% of cases). Causes of death were liver degeneration in 22 patients (61.2%), digestive hemorrhage in 8 patients (22.2%), hepatic encephalopathy in 3 patients (8.3%) and an infectious complication in 3 patients (8.3%).

4. Discussion

Cirrhosis remains a major cause of morbidity and mortality in the world despite the breakthroughs made in its prevention, particularly the treatment of hepatitis B and C [5].

Its prevalence varies depending on region. In our study, it was 6.2%. A previous Senegalese hospital study noted a prevalence of 9.1% [6]. In 2017, in the world, 10.6 million prevalent cases (10.3 - 10.9) of decompensated cirrhosis were registered and 112 (107 - 119) prevalent cases of compensated cirrhosis.

In France, prevalence varied between 0.3 and 0.6% [5]. Cirrhosis represented 33.9 et 22.6% of hospitalization motives respectively in Burkina Faso [7] and in Benin [8].

Male predominance was largely noted in published data [4] [7]-[14]. The young age of our patients was also found in other studies, notably in Africa [4] [6] [7] [8] [14]. The age of cirrhotic patients varies depending on the geographical zone and the etiology. Indeed, the disease appears at advanced age in regions where chronic alcohol use is predominant, and earlier in zones where hepatitis B infection is endemic [11] [12] [13].

Time to consultation delay was 6.2 weeks (44 days). It was 99 days in Guingané's study in Burkina Faso [7]. This long delay can be associated with, on one hand, the disease's clinical latency particularly during the compensated phase in which the patient is asymptomatic or presents minor symptoms, and on the other hand, the resort to traditional medicine and phytotherapy which can accelerate liver dysfunction. It was hepatitis B induced cirrhosis in 81.9% of cases. In Senegal 10% of the population are chronic carriers of HBS Ag and other studies have shown it is the first cause of cirrhosis [6] [15].

Prescription of Tenofovir Disoproxil Fumarate (TDF) has resulted in the improvement of the liver function in some patients marked by a decrease of the Child-Pugh score.

Treatment of the etiology changes significantly the disease's natural history. Marcellin *et al.* showed that long term TDF therapy led to fibrosis regression in hepatitis B virus induced cirrhosis [16] [17].

5. Conclusion

Liver cirrhosis is a frequent pathology in the hepato-gastroenterology department of the hospital Aristide Le Dantec in Dakar. It occurs more often in young male adult. Hepatitis B virus is the principal cause. TDF is an effective treatment enabling regression of the disease. However, the carcinogenic character of the HBV and preneoplastic of cirrhosis necessitate a prevention that requires an effective immunization policy against the hepatitis B virus and the management of hepatitis B infection.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 324-329
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

A Case Report on Duodenal Variceal Bleeding Treated with Glue Injection

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How to cite this paper: Neang, N., Vithiarithy, C., Khounthai, K., Viseth, K., Panha, M., Panha, U., Seiha, U., Sokchay, U., Keoseyla, U., Dimanche, C., Sovannvireak, K., Kimyi, K., Tharuom, N. and Syphanna, S. (2022) A Case Report on Duodenal Variceal Bleeding Treated with Glue Injection. *Open Journal of Gastroenterology*, **12**, 324-329.
https://doi.org/10.4236/ojgas.2022.1211033

Received: September 2, 2022
Accepted: November 1, 2022
Published: November 4, 2022

Abstract

Introduction: We present a case of upper gastrointestinal bleeding in a woman aged 56 years with liver cirrhosis who was diagnosed with isolated duodenal variceal bleeding, which was successfully treated with histoacryl injection. **Case Presentation:** A 57-year female cirrhotic patient presented with melena. She had been diagnosed with duodenal variceal bleeding and treated successfully with 2.4 ml histoacryl using a normal gastroscope. The patient subsequently remained stable and free of any further GI bleeding. She was discharged 48 hours later. Her hemoglobin remained stable at 9 g/L. **Conclusion:** The histoacryl glue injection provides an effective treatment. Hence, this should ideally be performed by an experienced endoscopist who is aware of and vigilant for the serious complications of this treatment option.

Keywords

Upper Gastrointestinal Bleeding, Portal Hypertension, Duodenal Variceal Bleeding, Glue Injection

1. Introduction

Portal hypertension is the progressive complication of liver cirrhosis and gives rise to the development of portosystemic collaterals commonly at the esophagogastric junction, the abdominal wall, and the rectum. Ectopic varices are a term reserved for varices that exist outside the esophagogastric region. Around 17% of ectopic varix, occur in the duodenum with the most common site of duodenal varices being the duodenal bulb, followed by the descending part of the duodenum. The bleeding provoked by ectopic dilated veins is reported for about 5% of

portal hypertension bleeding, however, the mortality rate can touch 40%. The present clinical treatment ways for bleeding from duodenal varix include medical drug treatment, surgical treatment, endoscopic treatment (endoscopic band ligation or sclerotherapy glue injection), and interventional embolization [1]. Though, there are no standard guidelines for the treatment of ectopic duodenal variceal bleeding. Our objective is to report a case of ectopic duodenal variceal bleeding treated successfully with histoacryl injection in our center in Cambodia.

2. Case Presentation

A 56-year-old female patient presented with melena. She had been diagnosed with alcoholic liver cirrhosis with a history taking of traditional medication.

At the time of admission, the patient's blood pressure was 99/60mm Hg, pulse rate was 102 per minute, respiratory rate was 20 per minute and basal body temperature was 37˚C. Physical examination showed an acutely ill appearance with mild confusion. The patient had conjunctival pallor, no scleral icterus, and no abnormalities on chest auscultation. The abdomen was soft to palpation but was distended, and there was tenderness to palpation at the epigastrium without rebound tenderness.

Laboratory findings showed hemoglobin concentration of 5.0 g/dL, leukocytes 14.07 K/μL (neutrophils 76%), and platelets

Serum biochemistry showed albumin concentration 2.0 g/dL, total bilirubin 0.52 mg/dL, aspartate aminotransferase 96 IU/L alanine aminotransferase 13 IU/L, creatinine 9.7 mg/L, blood urea nitrogen 35 mg/dL, prothrombin time 27% (international normalized ratio, 2.84), while all of hepatitis B surface antigen, hepatitis B surface antibody, and anti-hepatitis C virus were negative (see **Table 1** below).

Table 1. The initial labs result.

TEST	RESULT
White blood cells (WBC)	14.07 K/μL
Hemoglobin	5.0 g/dL
Platelet	145 K/L
Albumin	2.0 g/dL
Total bilirubin	0.52 mg/dL
Aspartate aminotransferase	96 IU/L
Alanine aminotransferase	13 IU/L
Creatinine	9.7 mg/L
Blood nitrogen urea	35 mg/dL
Prothrombin time	27%
Hepatitis B surface antigen	Negative
Hepatitis C anti-body	Negative

After resuscitation, an emergency upper gastrointestinal endoscopy was performed on the day of the patient's admission. It showed grade I esophageal varices without red color sign from all along the mid to lower esophagus. Apart from signs of congestive gastropathy, there were no other lesions suggestive of bleeding. Along the entire wall of the duodenal descending part was a pulsating blue varix with oozing bleeding (Figure 1). This was considered to be a bleeding focus, so the glue injection was performed without immediate complication. At our center, 0.5 mL glue aliquots (histoacryl) are mixed with 0.8 mL of lipiodol in small syringes. First, saline is injected into the variceal lumen to confirm an intra-luminal position at this point.

Then Glue/lipiodol mixture is injected 2.4 mL at a time (Figure 2). Further saline is instilled which separates the glue from the end of the needle and decreases the risk of tearing the glue through the variceal wall on removal of the needle. The hemostasis was achieved successfully with single session injection using a normal gastroscope. The patient subsequently remained stable and free of any further GI bleeding. She was discharged 48 hours later. Her hemoglobin remained stable at 9 g/L without any bleeding manifestation during follow-up within 6 months.

3. Discussion

The duodenal varices, first described by Alberti [2]. The prevalence of duodenal varices is associated with the cause of portal hypertension and the technique used to display the varices; up to 40% of patients with portal hypertension undergoing angiography showed duodenal varices. Although the frequency of bleeding is

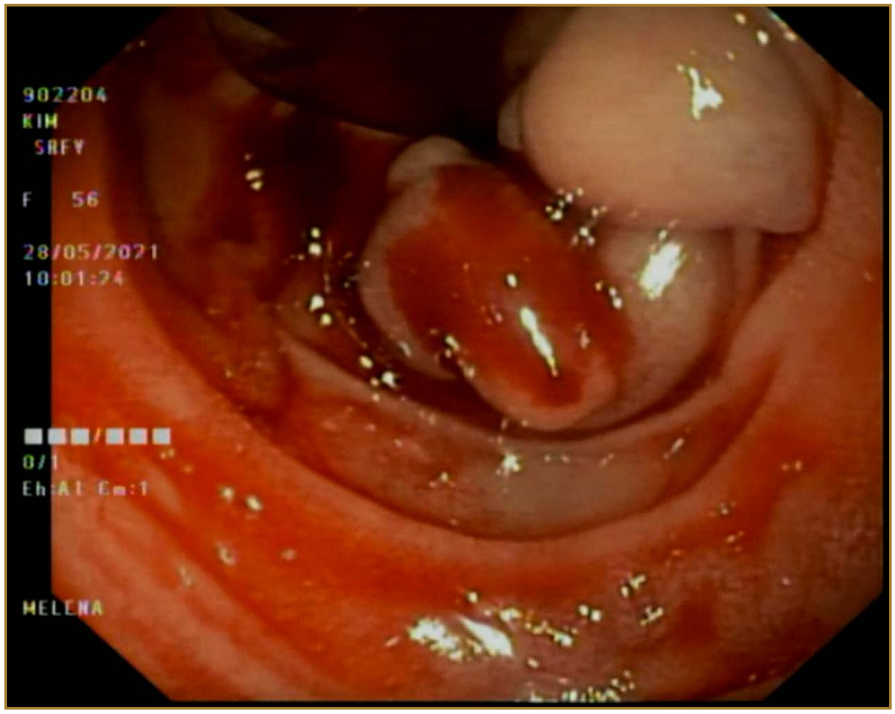

Figure 1. Nodular aspect of descending duodenum (D2) with oozing bleeding on dilated vein.

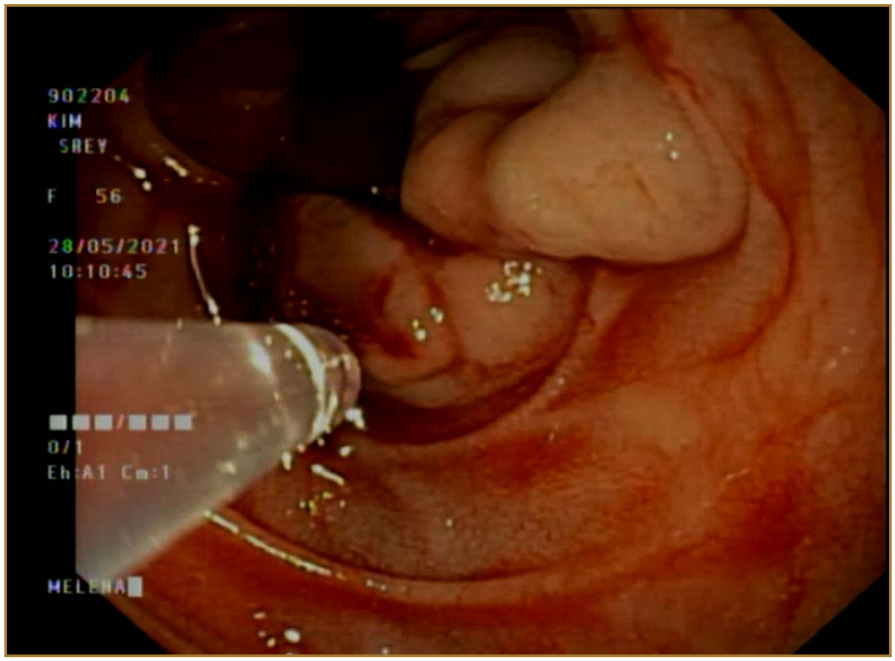

Figure 2. Glue injection on dilated vein with oozing bleeding.

low, when it does bleed, it can be fatal with a mortality of 35% to 40% [1]. The most common cause (30%) of duodenal varices is portal hypertension due to liver cirrhosis. Other causes include occlusion of the splenic vein due to pancreatitis, tumors, or thrombosis (25%), and occlusion of the portal vein due to thrombosis, infection, and tumors (25%) [3].

In our case review, the clinical characteristics of patients with duodenal variceal bleeding included the following: 1) cirrhosis-related intra-hepatic portal hypertension that was the main cause of patients with duodenal variceal bleeding; 2) the most frequent location of duodenal varices was the descending portion of the duodenum; 3) a majority of patients with duodenal variceal bleeding (53.5%) occurred in conjunction with gastric varices or esophageal varices.

Those clinical characteristics were comparable to the recent systemic review study conducted by Wan Yipeng *et al.* published in 2021 [4].

The etiology and position of duodenal varices persist debated. In Western countries, duodenal varices located in the duodenal bulb were found most frequently followed by duodenal varices located in the descending part of the duodenum [5] [6]. In contrast, in Asian countries, such as Japan and China, the descending part of the duodenum was the main location of duodenal varices followed by the duodenal bulb [7] [8] [9]. Remarkably, in Western countries, extra-hepatic portal hypertension was the most common cause of ectopic varices; on the other hand, cirrhosis-related portal hypertension was the most frequent cause in Asian countries [8] [9]. This difference may be related to the different causes and ethnicities of patient populations [10].

Regarding the treatment, medical therapy always comes first to resuscitate and stabilize the patient's condition just like in our case that we preferably do it be-

fore an endoscopy. In the past, surgical treatment methods such as variceal ligation, variceal excision, splenorenal shunting, and partial duodenectomy were used, but the rate of postsurgical mortality was as high as 30% and such methods are not commonly used in recent years. Recently, sclerotherapy, endoscopic ligation, and radiological intervention procedures as well as TIPS and balloon-occluded retrograde transvenous obliteration have been used for treatments [11]. In our center, we performed glue injection with the combination of cyanoacrylate (histoacryl) and lipiodol that is similar to the study done in Portugal conducted by Mariana Costa *et al.* [12]. Bhagani S *et al.* has published also the successful bleeding control done by glue injection on duodenal bleeding site with the same quantity of histoacryl with 2.4 ml as our center [13]. More recently in 2021, there was a systemic review that confirmed this hystoacryl glue injection in term of control of the bleeding due to duodenal variceal bleeding [14].

4. Conclusion

We all know that the injection of histoacryl glue is effective in terms of stopping the bleeding from duodenal varix but its harmful effect needs to take into account. In our case, we did not see any complications especially related to pulmonary embolism. Hence, this should ideally be performed by an experienced endoscopist.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 330-335
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Rectitis Radiation a Problem of Therapeutic Management in Senegal about Two Cases

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How to cite this paper: Fall, A.B., Niang, N., Yauck, A., Sidibe, M. and Fall, M.P. (2022) Rectitis Radiation a Problem of Therapeutic Management in Senegal about Two Cases. *Open Journal of Gastroenterology*, **12**, 330-335.
https://doi.org/10.4236/ojgas.2022.1211034

Received: September 13, 2022
Accepted: November 14, 2022
Published: November 17, 2022

Abstract

Radiotherapy occupies an important place in the management of cancers of the pelvic-perineal organs, it is at the origin of the fact of the ionizing radiations of radiation proctitis which is most often revealed by hematochezia. Diagnosis is based on rectoscopy which highlights a telengiectatic proctitis aspect. The standard treatment is endoscopic and based on argon plasma electrocoagulation. We report two cases of radiation proctitis occurring a few months after radiotherapy. Case number 1: A 76-year-old hypertensive patient known to have a history of cancer of the cervix treated with radiochemotherapy, she was received in an array of hematochezia of medium abundance; total colonoscopy found an aspect of telengiectatic proctitis making retain radiation proctitis. She had benefited from medical treatment, however, after a two-month follow-up, there was a recurrence of rectal bleeding despite medical treatment, due to the unavailability of endoscopic treatment based on argon plasma, surgical treatment of a type of protectomy had been carried out on postoperative follow-up was marked by a regression of hemorrhage with the occurrence of a. Case number 2: An 87-year-old patient, hypertensive, with a history of prostate adenocarcinoma 3 years ago treated with brachytherapy and hormone therapy; he was hospitalized with hematochesia. Rectosigmoidoscopy found an aspect of telengiectatic proctitis. The diagnosis of radiation proctitis had been retained and the patient had received medical treatment. The short-term evolution was marked by an amendment of the hematochezia with a long-term recurrence requiring endoscopic destruction via the diathermic loop of the telengiectatic lesions with good evolution without relapse after the procedure. Conclusion: Radiation proctitis is a major side effect of pelvic radiotherapy. Management is very difficult in our regions due to the unavailability of endoscopic means, in particular argon plasma.

Keywords

Radiation Proctitis, Hematochesia, Telangiectasias

1. Introduction

Radiotherapy occupies a growing place in the treatment of cancers of the pelvic-perineal organs. Despite the precautions taken in carrying it out, local complications can occur, linked to the effects of ionizing radiation on the tissues [1]. The rectum is frequently affected by its side effects giving rise to radiation proctitis which is most often revealed by hematochezia [1]. We report two cases of radiation proctitis occurring within 6 to 12 months after radiotherapy aimed at pelvic tumor reduction.

2. Observation

Case number 1

This was a 76-year-old hypertensive patient known for 06 years on Amlodipine 10 mg (1 tab/d) with a history of cancer of the cervix approximately 16 months ago before which she had benefited from a radiotherapy a type of brachytherapy 60 g per week for 6 weeks and chemotherapy based on Cisplatin and Paclitaxel declared in tumor remission after 3 months of treatment; she was received in a table of rectal bleeding of average abundance occurring at the beginning of stool accompanied by dyschezia and fetid leucorrhoea. The physical examination on admission found clinical anemia, hypogastric sensitivity without defense or contracture, an alteration the general condition who 1, the digital rectal examination had not found hemorrhoidal prolapse or anorectal tumor. On the biological level, we noted on the numeration formula a hypochromic microcytic anemia at 7 g/dl, the liver and kidney tests were normal, esophagogastroduodenal fibroscopy found an aspect of erosive antral gastritis and total colonoscopy found an aspect of telengiectatic proctitis associated with non-specific erosive lesions, the rest of the colon was normal; biopsies had been performed and histology was in favor of non-specific fibrous proctitis ruling out neoplasia and a solitary rectal ulcer; the abdominal CT scan was normal and showed no signs of ischemic proctitis. The diagnosis of radiation proctitis had been retained in view of his history of radiotherapy and the telengiectatic appearance of the rectum on lower endoscopy; the patient had received a blood transfusion; rectal enemas of aluminum salts (4g/d) and corticosteroids (Prednisone 40 g/d). The short-term evolution (day 8) was marked by a regression of rectal bleeding but the persistence of dyschezia was still noted. After a two-month follow-up, there is a recurrence of rectal bleeding despite good compliance with medical treatment, a second lower endoscopy had been performed and had shown the same telengiectatic lesions as the first due to the severe impact of rectal bleeding and the unavailability of the endoscopic treatment based on argon plasma in our region a surgical treatment a type of protectomy had been carried out the postoperative follow-up was marked by a regression of the hemorrhage with the occurrence of a massive pulmonary embolism which took the patient.

Case number 2

This was an 87-year-old hypertensive patient known for 20 years on coveram

10 mg (1 tab/day); quit smoking 39 years ago at 20 packs/year; a history of prostate adenocarcinoma 3 years ago, before which he had received brachytherapy-type radiotherapy (number of grays not specified) for 12 weeks and chemotherapy; currently on cardox cp (1 cp in the evening); ditropam 5 mg (10mg/day); he was received in a table of hematochezia of moderate abundance occurring during defecation accompanied by constipation. The physical examination on admission found clinical anemia and a deterioration in the general state OMS1, rectal examination had found a prolapse stage III hemorrhoid; on the biological level, the blood count showed a normochromic normocytic anemia at 7.4 g/dl, the renal assessment was normal. The esophagogastroduodenal fibroscopy found an uncomplicated hiatal hernia associated with an aspect of erosive and pseudo nodular antral gastritis; rectosigmoidoscopy found an appearance of telengiectatic proctitis associated with millimetric ulcerations (Figure 1 and Figure 2). Histology was in favor of nonspecific chronic proctitis. The diagnosis of radiation proctitis had been retained and the patient had received a blood transfusion, rectal enemas of aluminum salts (4g/day) and corticosteroids and a laxative treatment based on lactulose, the short-term evolution was marked by an amendment of the hematochezia followed by a long-term recurrence requiring endoscopic destruction via the diathermic loop of the telengiectatic lesions with good

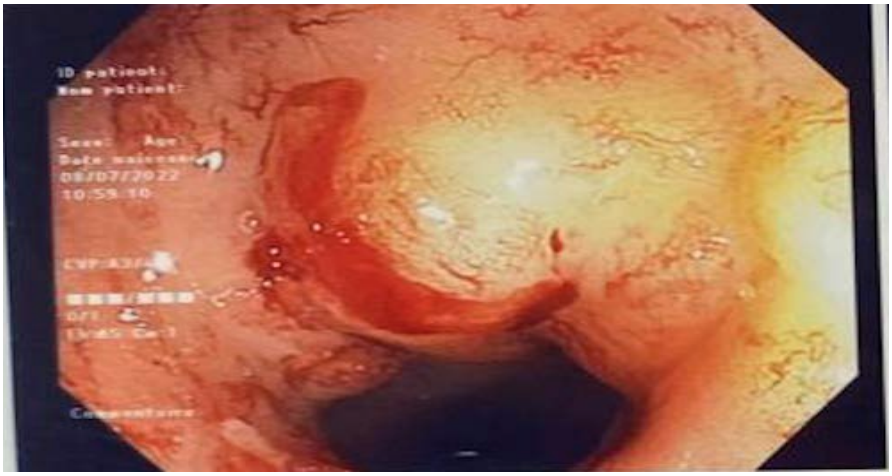

Figure 1. Aspect of telengiectatic proctitis (case number 2).

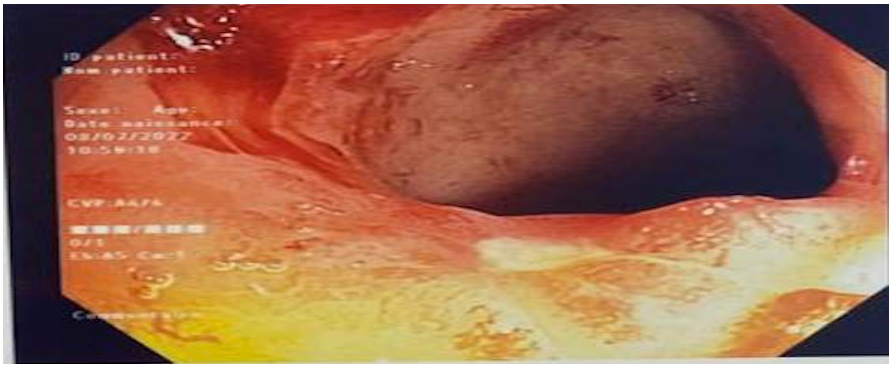

Figure 2. Appearance of telengiectatic and ulcerated proctitis (case number 2).

evolution without relapse after the procedure.

3. Discussion

Radiation proctitis is a radiation-induced rectal mucositis, occurring following radiotherapy of various pelvic malignancies [1] [2]. It is a rare pathology but its incidence is increasing due to the increasing use of curative radiotherapy. It occurs in 10% to 20% of patients after pelvi-pelvic radiotherapy within 6 to 24 months [3]. In our region only a few cases have been reported in the literature; Pathophysiologically, the pathogenesis of chronic radiation injury is complex. It involves stem cell destruction, progressive arteritis obliterans, and interstitial fibrosis reaching the full thickness of the rectal wall. These processes generate chronic, irreversible and progressive ischemia for years after radiotherapy with a possible tendency to extension. This results in superficial neovascularization in the form of mucous telangiectasias which will be responsible for bleeding [4]. The clinical manifestations are dominated by rectal bleeding, often moderately abundant at the start of stool, disabling, with clinical discomfort and haematological repercussions which may require iron supplementation or blood transfusion sessions [5]. Rectal bleeding is often associated with exemptions repeated and imperious, a tenesmus, false mucous needs [6]. In our patients, the main warning sign was rectal bleeding, which was disabling and was associated with dyschezia and false needs, thus requiring hospitalization. Several factors can contribute to the occurrence of radiation proctitis, namely a dosimetry exceeding 45 gy and the risk is higher when the dose exceeds 70 gy; mode of radiation therapy, brachytherapy has a higher risk than external beam radiation; time fractioning and spreading out the dose also increases the risk other factors unrelated to radiation therapy may contribute to the occurrence of radiation proctitis such as concomitant chemotherapy, clinical factors such as overweight, type 2 diabetes, advanced age (over 60), arterial hypertension, atherosclerosis and hypersensitivity to ionizing radiation of origin genetics [7] [8]. In our patients, the main risk factors found were a dosimetry greater than 45 gy, advanced age, diabetes, hypertension, overweight in case number 2, and brachytherapy in case number 1. Endoscopically the aspect of the rectal wall is variable, the most frequent presentation is a telengiectatic proctitis resting on a frosted and whitish mucosa, this aspect is often evocative and makes it possible to retain the diagnosis without histology [9], other atypical aspects can be found such as a congestive and erosive aspect sometimes an ulcerated aspect, these aspects must have biopsies carried out in order to eliminate a proctitis of infectious origin very frequent in our regions, a rectal adenocarcinoma or a proctitis of inflammatory origin in namely ulcerative colitis or Crohn's disease [10]. In our patients, the endoscopic appearance was diffuse telengiectatic proctitis with flame-like micro bleeding. In case number 2, the pathological examination of rectal biopsy fragments found nonspecific fibrous proctitis and in case number 1, nonspecific chronic proctitis. Medical treatment is often disappointing and relies on topical corticosteroids, sucralfate, sali-

cylates and short-chain fatty acids are all administered as an enema; antioxidant and healing drugs can be administered orally such as vitamins A, C, E, estrogen-progestogen combinations and Cholestyramine [11] [12]. Endoscopic treatment provides a better prognosis and is based on argon plasma electrocoagulation, laser photocoagulation, intra-rectal injection of formalin [13] [14]. Surgical treatment should be avoided as much as possible because of the extensive rectal fibrosis, the risk of bleeding and the risk of recurrence after surgery [15]. Our patients had benefited in first intention from a medical treatment based on sucralfate and corticosteroids in enema associated with a regularization of the transit; a favorable short-term evolution was noted in the 2 patients with a decrease in the frequency and abundance of rectal bleeding, however a long-term recurrence was noted in the 2 patients who subsequently motivated due to the unavailability in our counters of the curative endoscopic means the realization of a surgical protectomy with an unfavorable evolution in the case number 1 on the other hand the case number 2 had benefited from an endoscopic destruction of the lesions via the hot loop and the evolution was favorable with a regression bleeding. Thus the endoscopic destruction of telengiectatic lesions by the diathermic loop could be a therapeutic alternative in our regions insofar as endoscopic curative means are not available.

4. Conclusion

Radiation proctitis is a major side effect of pelvic radiotherapy. Several parameters (history of abdominopelvic surgery, diabetes mellitus, dosimetry) were listed, making it possible to identify patients at risk. The reference treatment is endoscopic and is based on argon plasma, the accessibility and technicality of which poses a problem in tropical environments.

Provenance and Peer Review

All authors have read and approved the document.

Consent

Patients gave consent to report cases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 336-346
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Immunohistochemical Profile of Human Epidermal Growth Factor Receptor 2 in Gastric Cancer in Rwanda

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How to cite this paper: Hategekimana, E., Ruhangaza, D., Hansen, C., Musoni, E., Rugwizangoga, B., Hammel, K., Gustavo, R.D., Mbarushimana, D., Nizeyimana, T., Twagirumugabe, T., Ndoli, J., Mukamana, F., Ngarambe, C., Habimana, E. and Weber, C. (2022) Immunohistochemical Profile of Human Epidermal Growth Factor Receptor 2 in Gastric Cancer in Rwanda. *Open Journal of Gastroenterology*, **12**, 336-346.
https://doi.org/10.4236/ojgas.2022.1211035

Received: October 31, 2022
Accepted: November 18, 2022
Published: November 21, 2022

Abstract

Background: Of the cancers diagnosed in Rwanda, stomach cancer is one of the most encountered. In fact, Rwanda belongs to the region where it is most incident in Africa. Most of the patients present with advanced disease. Studies showed that some gastric cancers overexpress Human Epidermal Growth Factor Receptor 2 (HER2/neu) protein and can be treated with Herceptin/Trastuzumab. This targeted therapy improves survival in patients with advanced disease. We conducted a study on Immunohistochemical profile of HER2/neu in gastric adenocarcinomas at two main Rwandan tertiary centers. **Methodology:** We tested for HER2/NEU in gastric adenocarcinomas diagnosed at University Teaching Hospital of Kigali (CHUK) and University Teaching Hospital of Butare (CHUB). Demographic and pathologic parameters were collected. Immunohistochemistry (IHC) for HER2/neu using c-erb/HER-2/neu (clone SP3) Rabbit Monoclonal antibody was done. Using the guidelines established by Hoffman *et al.*, the agreed score between 2 Rwandan pathologists and 1 USA pathologist was considered each time. Data were entered and statistically analyzed using SPSS 22. Descriptive statistical analysis method was

used. P-value calculated with Chi-square analysis for positive vs negative and equivocal negative to correlate HER2/neu overexpression with other variables across both hospitals. **Results:** A total of 286 cases were tested. HER2/neu overexpression (score 3+ or positive) was found in 29 cases (10.1%). 8 cases (2.8%) were equivocal negative (score 2+) while 249 cases (87.1%) were negative (score 0 and 1+). **Conclusion:** HER2/neu is overexpressed in a subset of gastric cancers in Rwanda, a phenomenon that has been reported in other areas of the world. Testing for HER2/neu could identify patients who would get a targeted treatment with Herceptin.

Keywords

Gastric, Cancer, Rwanda, HER2, Immunohistochemistry

1. Introduction

Rwanda, the landlocked Country in East Africa. The year 1994 marked a violent period of genocide against Tutsis that devastated the people and the infrastructure. Steps have been taken to reduce poverty and improve the overall wellbeing of people in order to decrease deaths then related mainly to communicable diseases. However, improved living conditions as days go on with unhealthy diet, some infections, physical inactivity and genetics have led to a rise in non-communicable diseases (NCDs).

Globally, stomach cancer ranks fourth of all diagnosed cancers and the second of all cancer related deaths with approximately 738,000 deaths each year attributed to this disease [1] [2]. The overall incidence of stomach cancer is rising in sub-Saharan Africa [3]. The western region of Africa has the lowest number of new cases, while the incidence is higher in Rwanda, Burundi, Southwestern Uganda, and the Eastern Kivu province of Democratic Republic of Congo [3] [4]. The Research which investigated the frequency of malignant tumors in former southern prefecture of Butare-Rwanda in 1994 revealed that stomach cancer accounted for 9% of all cancers diagnosed [5]. Globally, in 2020, Globocan report showed that gastric cancer was the 4th most incident cancer with 5.6% of all new cases of cancer. A study done in 2016 at the University Teaching Hospital of Kigali (CHUK) showed that gastric cancer was the most diagnosed malignant neoplasm of the gastrointestinal tract (GIT) and accounted for 65.3% of GI malignancies diagnosed in 2015 (Felix Manirakiza: Clinicopathological Characteristics of GIT lesions diagnosed at the Anatomic Pathology unit of CHUK, Thesis for Masters of Medicine in Anatomic Pathology, 2017). A recent study done at CHUB on upper GIT cancers showed that gastric cancer was the most diagnosed comprising 92% of all upper GIT cancers [6].

Surgery yields satisfactory patient outcomes when gastric cancer is diagnosed early; however, most cases seen in Rwanda are diagnosed at an advanced stage which includes inoperable local disease, recurrent disease, and/or metastatic dis-

ease [7]. Delayed medical consultation is thought to be a contributing factor. Once the disease has been deemed distant stage, treatment options are limited and the 5-year survival rate is very low [1] [8]. HER2/neu is a receptor that weighs 185 kDa and belongs to the HER family of receptor tyrosine kinases [9]. A study called the potential for targeted therapies among gastric tumor patients at Kigali University Teaching hospital showed targetable mutation in PTEN gene [10]. HER2 encoding gene is situated on the chromosome 17 and is an oncogene. Its overexpression leads to the development of cancer. This oncogenic mechanism was first identified in breast cancer in 1985. In 1986, the identification of HER2/neu protein in stomach cancer was first described [9] [11] [12]. Subsequently, it has been also found in carcinomas of ovary, lung, colon and prostate [13] [14].

The unfavorable prognosis of people with advanced stomach cancer has led oncology researchers to try to identify an adjunctive therapy that improves patient survival [15] [16] [17]. Targeted therapy refers to the utilization of medicines that are directed against specific errors within cancer cells. Trastuzumab, Ramucirumab, imatinib are some of the drugs used. Subsequently, it has been also found in carcinomas of ovary, lung, colon and prostaste [18] [19].

Many researches have showed HER2/neu protein overexpression and its gene amplification in 4% - 53% (median 18%) of gastric and gastroesophageal junction cancers [20] [17] [18]. A study done in Kenya at Kenyatta National Hospital showed that 42.4% of cases of gastric and gastro-esophageal junction carcinoma overexpressed HER2/neu while a study done in South Africa about HER2/neu in gastric carcinoma showed HER2/neu positivity in 12% of examined cases [12] [18]. A multi-national study demonstrated HER2/neu overexpression of 20% in gastric GEJ cancers [20]. The research study Trastuzumab for Gastric Cancer (ToGA) is in its phase three, and revealed increased survival in people with HER2/neu positive advanced gastric cancer when Trastuzumab/Herceptin is added to previously established chemotherapy regimens [9]. Many other countries now perform routine testing of HER2/neu on all cases of gastric adenocarcinoma (GAC), as well as utilize trastuzumab for treating of HER2/neu positive advanced stomach cancer [9]. In Africa there is insufficient research regarding HER2/neu testing in stomach and gastroesophageal junction carcinomas. No substantial research on IHC profile of HER2/neu in GACs has been done in Rwanda. Our goal was to evaluate HER2/neu protein overexpression in GAC patients in two main tertiary centers of Rwanda to identify the percentage of patients that could experience improved survival with advanced gastric cancer using Trastuzumab treatment.

2. Methods

Study design and cases selection

We performed a mixed retrospective and prospective, descriptive study of patients diagnosed with GAC on gastric biopsies or resections at CHUK from Jan-

uary 2015-December 2016 and at CHUB from January 2017-March 2022.

Settings

CHUK and CHUB are the two main tertiary University Teaching Hospitals in Rwanda, with a combined capacity of 1000 beds and 1200 workers. 6000 histopathology and 3000 cytopathology cases are diagnosed per year. Butaro District Hospital is a hospital in the North of the country and is a cancer center of excellence equipped with digital pathology services.

Data extraction and IHC Process

Hematoxylin and eosin (H&E) stained slides, paraffin blocks, pathology examination request forms, and pathology reports were retrieved from the archives of the anatomic pathology units at both hospitals. Demographic and pathologic information was retrieved from each patient's pathology examination request forms and open clinic records. The H&E stained glass slides were reviewed on light microscopy by three Rwandan pathologists (one at CHUK and two at CHUB) in order to confirm the diagnosis and type of GAC (according to Lauren *et al.*) and select appropriate block for HER2/neu IHC staining. Once the paraffin block was chosen for each case, they were used to cut unstained sections for HER2/neu IHC. For cases from CHUK, the process of manual IHC was done in the anatomical pathology laboratory of Butaro Cancer Center of Excellence in 2018 while cases from CHUB were manually performed at CHUB in 2022. Both laboratories utilized HER2/neu IHC with c-erb/HER-2/neu (clone SP3) Rabbit Monoclonal antibody Cat.#RM-9103-S0, -S1, or-S (0.1 ml, 0.5 ml, or 1.0 ml Supernatant) by DAKO (Santa Clara, California, USA). Each time, IHC slides were read by 2 Rwandan pathologists and then use digital slide scanner to send them for review by 1 USA based pathologist. Using the guidelines of Hoffman *et al.* [17]. The agreed score between these 3 pathologists through regular discussion was retained.

Statistical analysis

The data collected using a premade questionnaire were entered into an excel spreadsheet and analyzed using SPSS version 22. Descriptive statistical analysis method was used to describe age, gender, type of specimen, type of adenocarcinoma, stage of disease and HER2/neu overexpression in frequency and percentage for each hospital. P-value calculated with Chi-square analysis for Positive vs negative and equivocal negative to correlate HER2/neu overexpression with other variables across both Hospitals.

Strength

This is the first study of its kind to be carried out in Rwanda. We feel it has opened the door to larger and more in-depth studies of HER2/neu expression in gastric adenocarcinoma, as well as lead to the potential initiation of routine HER2/neu immunohistochemically testing in all cases of gastric adenocarcinoma. Identification of patients who are eligible for treatment with Herceptin will hopefully lead to increased survival in a subset of people with advanced stomach adenocarcinoma.

Limitations

The in-situ hybridization (ISH) technique which normally helps to sort out equivocal cases, is not available in our laboratories. Accordingly, some cases of HER2/neu positive gastric adenocarcinoma may have been missed.

Most of this study is retrospective, there is no way we could remedy some of the inconveniences that might have been caused by some errors in pre-analytical phase like prolonged fixation and ischemic time.

3. Results

The total number of tested cases was 286, including 143 cases from CHUK and 143 cases from CHUB. A total of 29 cases were positive (10.1%) (Figure 1), a total of 8 cases were equivocal negative (2.8%) (Figure 2) while a total of 249 cases were negative (89.7%) (Figure 3, Table 1).

Among positive cases; 26 (89.7%) were biopsies while 3 (10.3%) were resection specimens, 18 (62.1%) were intestinal type as per Lauren and 7 (24.1%) were diffuse while 4 (13.8%) were mixed type, 1 (3.4%) was early gastric cancer, 2 (6.9%) were locally advanced gastric cancer and 26 (89.7%) were not staged, 11 (37.9%) were males while 18 (62.1%) were females, 10 (34.4%) were aged less or equal to 50 years old while 19 (65.6%) were more than 50 years old (Table 2).

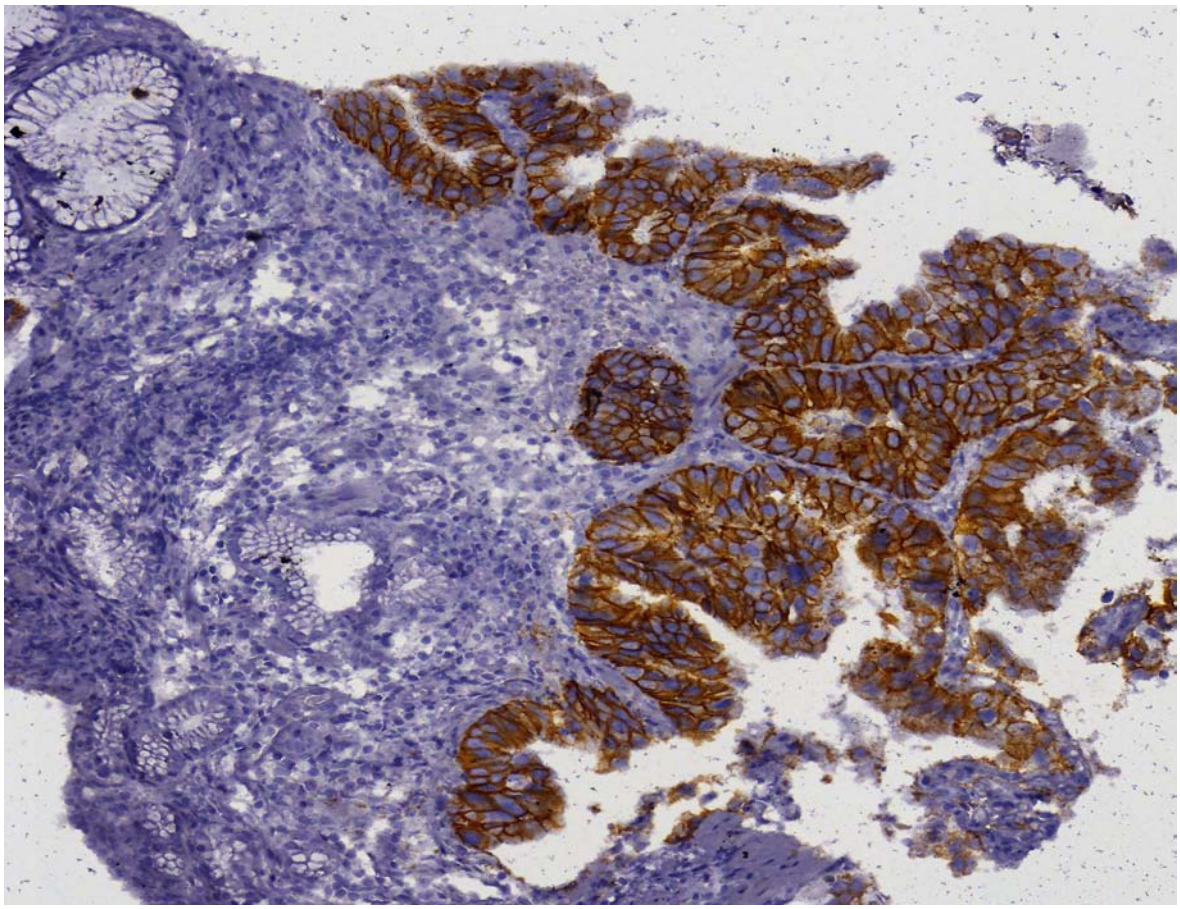

Figure 1. Immunohistochemistry stain. HER2/neu score 3+: Positive/Overexpression.

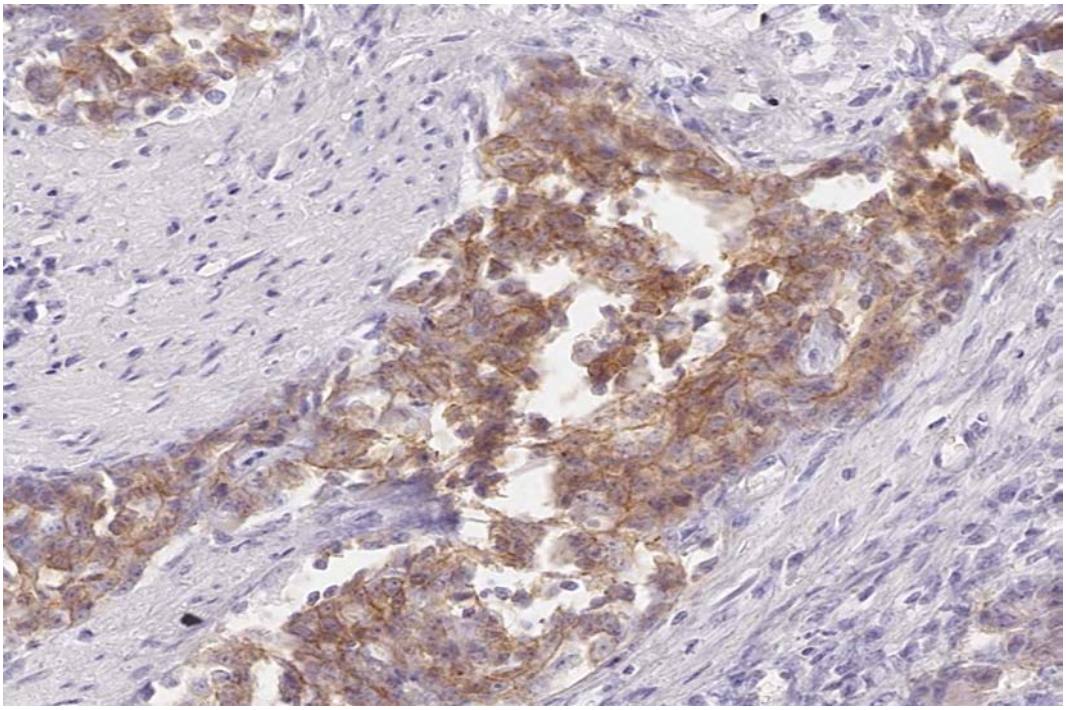

Figure 2. Immunohistochemistry stain. HER2/neu Score 2+: Equivocal negative.

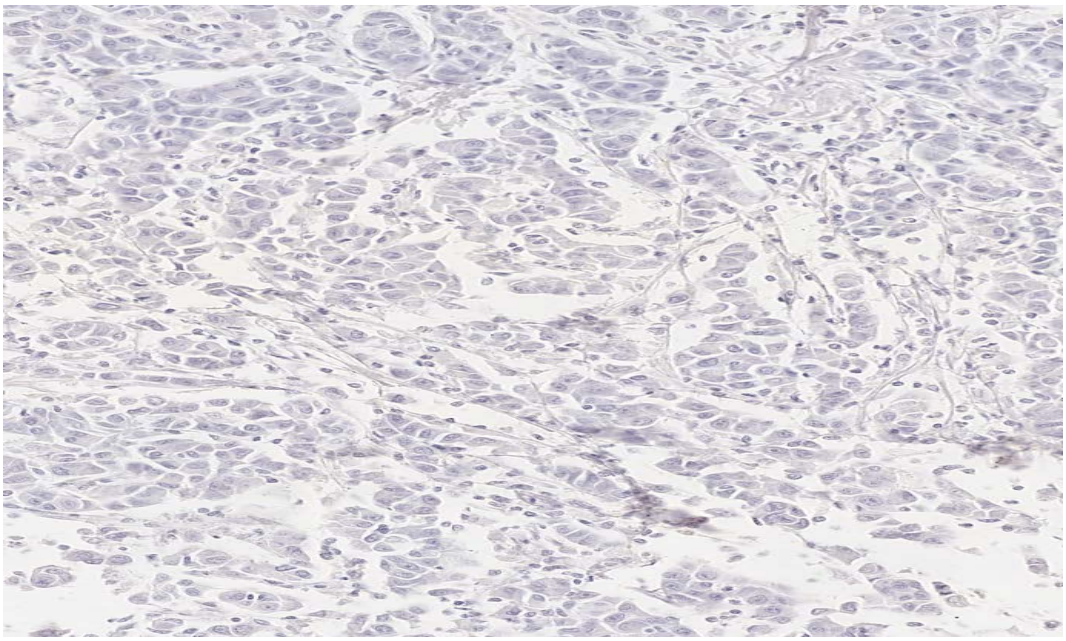

Figure 3. Immunohistochemistry stain. HER2/neu Score 0: Negative.

Table 1. HER2/neu overexpression.

HER2/neu Overexpression	CHUK n = 143 (%)	CHUB n = 143 (%)	Total N = 286 (%)
Negative	126 (51)	123 (49)	249 (89.7)
Equivocal Negative	7 (88)	1 (12)	8 (2.8)
Positive	10 (34)	19 (66)	29 (10.1)

Table 2. Association between demographic and clinical pathology characteristic with Her2/neu overexpression.

Variable name N = 286		HER2/neu overexpression (CHUK) n = 143			HER2/neu overexpression (CHUB) n' = 143			P-value
		Positive	Equivocal negative	Negative	Positive	Equivocal Negative	Negative	
Age (years)	≤50	5	0	42	5	1	37	0.359
	>50	5	7	84	14	0	86	
Gender	Male	2	5	63	9	1	59	0.225
	Female	8	2	63	10	0	64	
Type of specimen	Biopsy	9	6	113	17	1	109	0.928
	Resection	1	1	13	2	0	14	
Type of adeno-carcinoma	Intestinal	5	5	65	13	0	64	0.08
	Diffuse Mixed	4 1	2 0	52 9	3 3	2 0	53 6	
Stage	Early	0	0	0	1	0	3	0.565
	Locally advanced	1	1	13	1	0	10	
	Not applicable	9	6	113	17	1	110	

P-value calculated with Chi-square analysis for Positive vs negative and equivocal negative.

4. Discussion

Our study showed that 10.1% of gastric adenocarcinomas overexpressed HER2/neu protein in addition to other targetable PTEN mutation described by Oscar [10]. This percentage is within the widely variable range of HER2/neu overexpression described in various population across the globe ranging from as low as 4% described in England in 2010 by Grabsch [21] to as high as 53.4% described in Germany by Allgayer in 2000 [11] [22]. In India, a study done By Indu Rajagopal showed that 22.4% of the tumors overexpressed HER2/neu while another done by Prachi SPatil *et al.* revealed 7% of cases overexpressing HER2/Neu [17] [23]. A systematic analysis comprising 17,338 cases published in 48 articles has showed a mean HER2/neu overexpression at 17.9% [24]. A study done at Kenyatta National hospital showed HER2/neu overexpression in 42.2% of 66 cases while a study from South Africa showed HER2/Neu overexpression in 12% of 97 cases studied [12] [18].

The association between HER2/neu overexpression and age was not statistically significant in our study (P-value: 0.359). This is probably due to few positive cases in our research. No significant association with age found also in a study done at Kenyatta National Hospital as well as the study done in Brazil by Renato Santos Laboissiere [12] [25].

No relationship between gender and HER2/neu overexpression in our study (P-value: 0.225). This finding is the same as what was found in a study done at Kenyatta hospital, in Brazil by Renato and in china by SD Xie [12] [25] [26].

No association between HER2/neu overexpression and type of specimen (P-value: 0.928). However, many of HER2/neu positive specimens were biopsies than resection specimens the same as described in the research done in India by Indu Rajagopal [17].

No statistical relation between type of adenocarcinoma and HER2/neu overexpression (P-value: 0.08). This is again thought to be related to the small number of positive cases in this study. This finding is different from many studies like in India by Rajagopal, in South Africa by Roberts and in Brazil by Renato, where significance was found [17] [18] [25]. On the other hand, there was a greater number of intestinal type HER2/neu positive cases compared to diffuse and mixed types, the same as found in a study done at Kenyatta Hospital [12].

No statistical significancy found also between HER2/neu overexpression and the cancer stage (P-value: 0.565).

5. Conclusion

Stomach cancer is deadly worldwide and belongs among the most frequently diagnosed cancers in Rwanda. Its late diagnosis at advanced stage leads to a poorer prognosis due to limited treatment options. Our study has demonstrated that 10.1% of tested cases had HER2/neu protein overexpression. Hence, some of them may benefit from targeted therapy. Immunohistochemistry for HER2/neu in gastric adenocarcinomas can be technically done and interpreted in Rwanda, however In situ hybridization is needed to sort out equivocal cases.

Data Availability Statement

The dataset is available from the author whenever there is a reasonable need.

Funding Statement

This research was funded by the University Teaching Hospital of Butare, Bio-Ventures for Global Health and American Society of Clinical Pathology.

Ethics Approval Statement

After approval in pathology departments, we got approval from institution review boards of CHUK and CHUB

Patient Consent Statement

No consent was signed by patients as we got approvals by both hospitals to retrieve data in their archives.

Acknowledgments

I would like to thank and aknowledge the contribution of all my co authors, the staff of pathology departments of CHUB, CHUK, Butaro District Hospital without who this study could not have been completed. Let me thank also The University Teaching Hospital, Bioventures for Global Health and American Society

of Clinical Pathology for their financial contribution.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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