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Lymphocytic colitis: an Important but Underdiagnosed Cause of Chronic Diarrhoea in Adult Nigerians

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Introduction: Lymphocytic colitis is an important cause of chronic diarrhoea which is amenable to appropriate treatment which helps to reduce the morbidity and mortality associated with chronic diarrhoea. In Africa unfortunately, there is poor awareness of this treatable cause of chronic diarrhoea on account of a paucity of skilled experts necessary to make a diagnosis and implement effective therapy.

Aim: We present the clinical aspects, endoscopic findings and pathological features of twenty-one Nigerian patients with lymphocytic colitis. A short literature review of the epidemiological, clinical, endoscopic, and pathological features of this important condition is also presented.

Materials and Methods: This was a retrospective analysis of the clinical, endoscopic and pathological findings of twenty-one patients who were diagnosed with lymphocytic colitis following colonoscopy in an open-access endoscopy setting in Akure, Ondo State, Nigeria over eighteen months.

Results: Twenty-one diagnoses of lymphocytic colitis were made from a pool of one hundred and twenty-two colonoscopies done between December 2021 and May 2023. There were slightly more females diagnosed with an M: F ratio of 3:4 with a mean (SD) age of 52.2 (± 14.3) years. All of the patients had a history of passage of watery diarrhoea while normal colonoscopy findings were present in 87.5%. The mean (SD) time to diagnosis in five of these study subjects was 18.4 ± 9.1 months. These patients had standard medical treatment with good outcomes.

Conclusion: In sub-Saharan Africa, lymphocytic diarrhoea is a treatable cause of chronic diarrhoea. It is important to refer patients with chronic diarrhoea to facilities where they can benefit from the expertise of endoscopists and pathologists.

Keywords: Lymphocytic colitis, chronic diarrhoea, Nigeria

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Introduction

Chronic diarrhoea is one of the most common presentations in the Gastroenterology clinic. [1] Aside from infectious diarrhoea, it is increasingly becoming more apparent that lymphocytic colitis is an important cause of diarrhoea. [1] Lymphocytic colitis was described by Read and Lazenby as part of the entity called microscopic colitis, which also includes collagenous colitis. [1] Though lymphocytic colitis is an established cause of chronic diarrhoea, there are only sparse reports of it in Africa. [2,3] This is largely due to the shortage of skilled personnel required to make the diagnosis. [4,5] It is important to make the diagnosis of lymphocytic colitis in patients with chronic diarrhoea as treatment options are available to reduce the significant morbidity associated with the disease.

Materials And Methods

A retrospective analysis of prospectively collected data of patients with a diagnosis of lymphocytic colitis retrieved from the Endoscopy Register of an open access endoscopy setting in Akure, Ondo State, Nigeria as well as the outcomes of some of the patients who were consecutively afterwards seen in a Specialty Gastroenterology Clinic in Akure, Ondo State was carried out. The information obtained from the register between December 2021 and May 2023 (eighteen months) included the age and sex of the patients, indication and diagnosis. The study complied with all ethical protocols as contained in the Helsinki Declaration.

All the patients underwent a 2-day bowel preparation before the procedure. The bowel preparation consisted of a liquid diet, 30 mg of bisacodyl tablets, and Epsom salt solution. All patients signed an informed written consent before undergoing colonoscopy. Pre-medications were given to all the patients, which consisted of intravenous midazolam 2.5–5 mg and pentazocine 30 mg. The patient's vital signs were monitored before, during, and after the procedure. A digital rectal examination was carried out on all the patients before the insertion of the colonoscope. The Pentax EC-3890 LX Video colonoscope was used for the duration of the study. The procedures were carried out with the patient initially in the left lateral position. A change in posture and abdominal pressure were applied where necessary. Caecal intubation was defined as deep intubation into the caecum with visualization of the appendiceal orifice. Biopsies were taken and sent for histological examination.

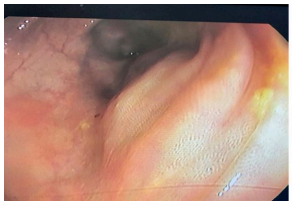
Histological examination of the biopsies was conducted and reviewed by seasoned histopathologists with expertise in this field. The diagnostic criteria used were as follows: lymphocytic colitis was recognized by an increased intra-epithelial lymphocyte content (greater than 20 per 100 epithelial cells) and an associated increase in inflammatory cells in the lamina propria but no thickened collagen band. Data Analysis All data were collated and analyzed using the statistical package for social sciences (SPSS) version 20.0 (IBM, Armonk, NY, USA). The ages of the patients were summarized using mean and standard deviation (SD). Variables such as ages, sex, colonoscopy indications, endoscopy findings, time to diagnosis and outcomes were presented in frequency tables.

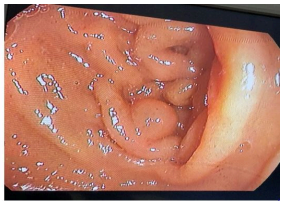
Results

The mean age (SD) of the studied population was 52.2 (± 14.3) years. There were 12 (57.1%) females and 9 (42.9%) males, with a male: female ratio of 3:4. The major complaint was the passage of loose stools (100%) while the commonest colonoscopy finding was normal-looking colonic mucosa (85.7%). Five of these patients were managed in the Gastroenterology Specialty Clinics and had good outcomes. The mean (SD) time to diagnosis in these five patients was 18.4 ± 9.1 years.

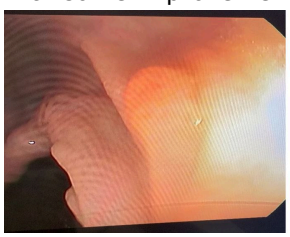
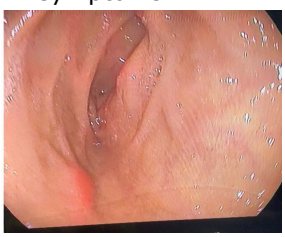
Summaries of patients seen in the Gastroenterology Specialty Clinic

Case 1: 52-year-old woman who presented on account of recurrent passage of loose stools which had been on and off for eighteen months. The stools did not resolve with over-the-counter medications. There was associated upper abdominal pain for which she used PPIs namely Rabeprazole. Endoscopy revealed an erythematous patch in the descending colon. There was oedema of the mucosa of the transverse colon. She was commenced on Prednisolone and Cholestyramine with improvement in clinical symptoms.

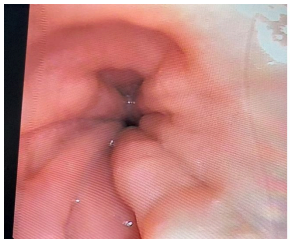
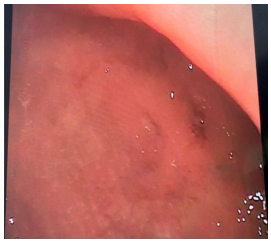




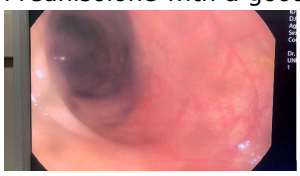
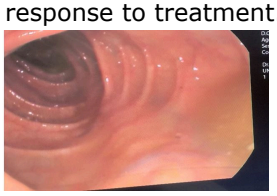
Case 2: 59-year-old woman who presented with a history of recurrent passage of loose stools of a year duration. She had been to several hospitals with improvement in symptoms. A colonoscopy revealed oedematous colonic mucosa with widespread patchy erythema. She was commenced on Prednisolone with some improvement in symptoms.

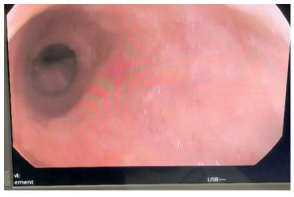
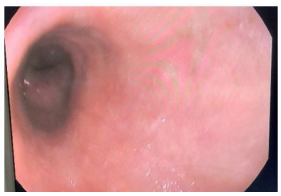
Case 3: 67-year-old male who presented on account of passage of loose stools of a year's duration. He is a known diabetic. The colonic mucosa was normal apart from healed ulcers in the rectal mucosa. He was commenced on Budesonide with significant improvement in clinical symptoms.

Case 4: 66-year-old woman with complaints of recurrent passage of loose stools of 14 months duration. The colonic mucosa was normal throughout on colonoscopy. She was commenced on Prednisolone with a good response to treatment.

Case 5: 21-year-old woman who had been passing loose stools for three years. On endoscopy, the colonic mucosa appeared normal. She was absent from school for a significant amount of time on account of frequent passage of loose stools.

She made remarkable improvements on steroids and is now able to pay more attention to her education.

Informed consent: informed consent was sought and obtained from the patients.

Table 1: Socio-demographic and clinical characteristics of patients

Sr.	Age (years)	Sex	Indication	Endoscopy findings	Time to diagnosis (months)	Outcome
1	68	F	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
2	75	F	Passage of loose watery stools. There was also a history of abdominal pain	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
3	64	F	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
4	50	M	Passage of loose watery stools. There was also a history of abdominal pain	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
5	44	M	Passage of loose watery stools and faecal incontinence	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
6	21	F	Passage of loose watery stools	Normal looking mucosa	36 months	Good
7	66	F	Passage of loose watery stools	Normal looking mucosa	14 months	Good
8	47	F	Passage of loose watery stools	Oedematous and erythematous colon	_____	Was not referred to the gastroenterology speciality clinic
9	57	F	Passage of loose watery stools. There was also a history of haematochezia	Normal-looking mucosa. Internal haemorrhoids	_____	Was not referred to the gastroenterology speciality clinic
10	40	M	Passage of loose watery stools. There was also a history of haematochezia	Oedematous and erythematous colon. Internal haemorrhoids	_____	Was not referred to the gastroenterology speciality clinic
11	67	M	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
12	35	F	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic

13	62	M	Passage of loose watery stools. Recurrent haematochezia	Normal-looking mucosa. Internal haemorrhoids	_____	Was not referred to the gastroenterology speciality clinic
14	67	M	Passage of loose watery stools.	Normal looking mucosa	12 months	Good
15	79	M	Passage of loose watery stools. Recurrent haematochezia	Normal-looking mucosa. Internal haemorrhoids	_____	Was not referred to the gastroenterology speciality clinic
16	46	M	Passage of loose watery stools. There was also a history of weight loss.	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
17	38	F	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
18	59	F	Passage of loose watery stools	Oedematous and erythematous colon	12 months	Good
19	52	F	Passage of loose watery stools	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
20	70	M	Passage of loose watery stools. History of chemotherapy for colorectal cancer	Normal looking mucosa	_____	Was not referred to the gastroenterology speciality clinic
21	52	F	Passage of loose watery stools	Normal looking mucosa	18 months	Was not referred to the gastroenterology speciality clinic

Mean ±SD

Age: 52.2 ± 14.3

Time to diagnosis : 18.4 ± 9.1

Range

Age: 21-75

Time to diagnosis: 12-36

Figures 1-6 highlight and describe some of the characteristic microscopic features found in lymphocytic colitis in one of the cases in this study

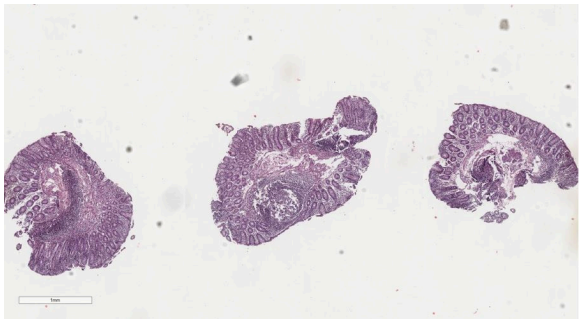


Figure 1: showing three bits of colonic tissue.

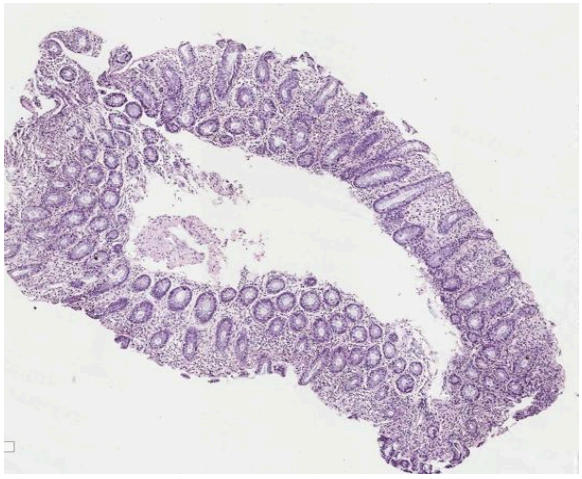


Figure 2: showing evidence of loss of gland and architectural distortion and oedema

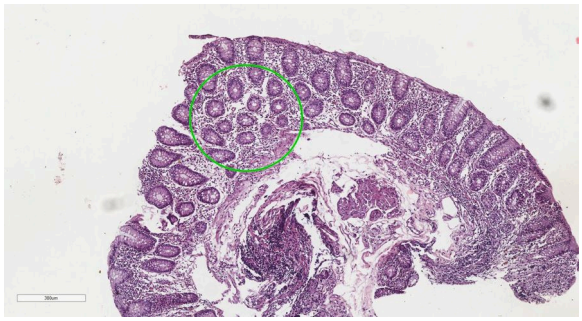


Figure 3: showing evidence of mild to moderate loss of gland and oedema (green circle)

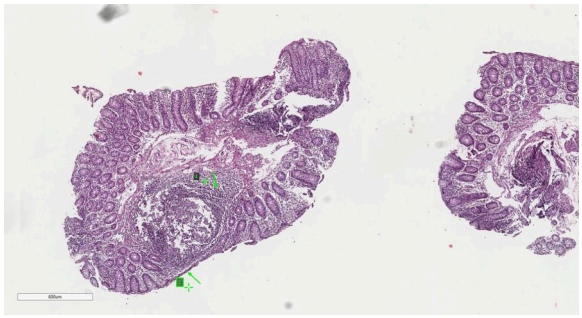


Figure 4: showing lymphoid aggregate with germinal centre (green arrow 1) and mucosal erosion (green arrow 2)

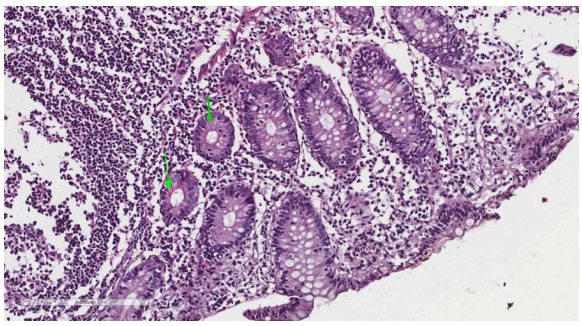


Figure 5: Showing loss of apical mucin (green arrow)

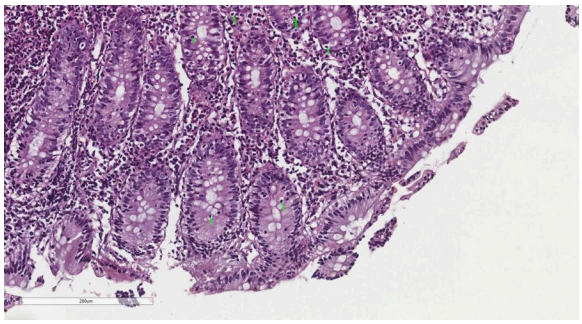


Figure 6: showing intraepithelial lymphocytes (green arrows)

Discussion

Chronic diarrhoea causes significant morbidity and mortality [6] The role lymphocytic colitis plays in the aetiology of chronic diarrhoea is increasingly being recognized and said to account for 10-20% of chronic diarrhoea.[7] The prevalence and incidence rates in developed economies are 0.5-12.9/100 000(8) and 2.3 to 16/100 000 respectively[9] [10] However, the incidence has been noted to plateau in the above-developed economies [11][12] The landscape in Africa has not been well described due to the paucity of skilled endoscopists, diagnostic facilities and histopathologists [4][5]. Nonetheless, case reports are beginning to describe it [2][3] The role of histopathologists in its diagnosis cannot be overemphasized as the diagnostic criteria for lymphocytic colitis which is intraepithelial lymphocyte ≥ 20 per 100 inter cryptal epithelial cells, change in surface epithelium (flattening and mucin depletion), mononuclear infiltration of the lamina propria as well as subepithelial collagen layer less than 10μm is within the realm of histopathology.[13] [14] It is important to define the role lymphocytic colitis plays in the aetiology of chronic diarrhoea in Africa as there is effective treatment for it.

In this study, there was a female preponderance as observed in previous studies [8][12] The average age was 55 years which was lower than the peak age of 65 years as has been previously described [7]. Indeed, 25% of patients with lymphocytic colitis are under 45 years old [15].All of them had loose, watery diarrhoea which is the classic presenting complaint [13][16]. Other symptoms found in some of the patients include weight loss, faecal incontinence and abdominal pain. It is important to note that other studies have recognized that the presentation can be myriad

Including symptoms like nocturnal diarrhoea, weight loss, urgency, faecal incontinence and abdominal pain [15][17] Four of the patients had a history of haematochezia in addition to the primary complaint of watery diarrhoea. In these patients, the additional finding on colonoscopy was internal haemorrhoids which could have been responsible for the bleeding per rectum. Oluyemi et al noted similar findings of co-existing haemorrhoids and haematochezia in patients who were diagnosed with lymphocytic colitis [3]. One of the patients who had presented for colonoscopy on account of chronic diarrhoea had a history of treatment of colorectal cancer. Studies have reported that patients treated with chemotherapeutic agents may develop lymphocytic colitis though the exact therapeutic agent(s) the patient in this index study received was not ascertained [18]. Conditions that have been documented as being associated with lymphocytic colitis include coeliac disease, uveitis, idiopathic pulmonary fibrosis, juvenile diabetes mellitus, pernicious anaemia, autoimmune thyroiditis and oligoarthritis [19][20][21] These associations are however more linked with collagenous colitis which is within the spectrum of microscopic colitis.(19) Genetic susceptibility in the HLA-DR3-DQ2 haplotype, altered epithelial barrier function and mucosal inflammation have been suggested as possible pathophysiologic mechanisms for lymphocytic colitis [22][23]

One of the patients was documented to have a history of chronic use of PPIs namely Rabeprazole for upper abdominal discomfort. It is interesting to note that PPIs in particular, lansoprazole have been particularly implicated in the causation of lymphocytic colitis.[1] Other drugs thought to play a role in the pathology of lymphocytic colitis include NSAIDs, statins, SSRIs, pembrolizumab and flutamide.[24] However, there is conflicting evidence as most of these drugs are also known to cause chronic diarrhoea.[25]

As has been noted previously, many patients are missed on initial presentation if proper evaluation is not done. [25] An earlier study showed how lymphocytic colitis can be mistaken for irritable bowel syndrome [2][25]. Indeed, one of the patients in this study had intermittent diarrhoea which can simulate irritable bowel syndrome. Chronic diarrhoea is however mostly first treated as infectious colitis in sub-Saharan Africa and expectedly, all of the patients in this study

Had a history of prior treatment with antibiotics before colonoscopy [26]. In this case series presented, the patients had a mean lag time of eighteen months before definitive diagnosis. This is in contrast to Europe where the median time to diagnosis is eight weeks [27]. This in no small regard contributes to the diminished quality of life that patients with lymphocytic colitis suffer as a result of their symptoms particularly unremitting diarrhoea [28]. This was seen in one of the patients who missed school on account of diarrhoea. Other debilitating features documented in patients with lymphocytic colitis include worry about losing control of bowel function, feelings of guilt and embarrassment, lack of social participation as well as impaired sexual functioning. [6]

The classical picture on endoscopy is normal colonic mucosa which was noted in the majority of the patients discussed. Colonic mucosal oedema and patchy erythema were noted on colonoscopy in three patients. Other endoscopic lesions that may be present include increased mucosal vascularity, ulcerations, erosions, mucosa friability and scars [21] We did not find any of these in this cohort of patients. The growing consensus is that samples should be taken from both sides of the colon, particularly the ascending and descending colon. [29][30] Part of the rationale behind this is that patients may sometimes present with patchy colitis. It is a diagnosis of exclusion as other causes of chronic diarrhoea such as ulcerative colitis and colorectal cancer have to be ruled out. It is important to note that these entities may also cause intraepithelial lymphocytosis [31].

Fortunately, the disease runs a benign course. As noted above, the patients who received treatment showed significant improvement in symptoms of steroids. Unfortunately, most of the patients could not be followed up as they were not referred to the gastroenterology speciality clinic by their primary managing physician. Most of the patients who received treatment were placed on Prednisolone as Budesonide which is the gold standard is not readily available. TNF alpha therapy has been suggested for patients with severe disease who do not respond to steroids or immunomodulators. [32]

Conclusion

This study provides more information on the clinicopathological presentations of lymphocytic Colitis in Nigeria and hopefully will increase awareness of this treatable cause of chronic diarrhoea. A limitation of this study is its retrospective nature such that we could not probe fully into the social, medical and drug histories of the patients. We hope that in the future additional studies which will be large-scale, longitudinal, and preferably, prospective will be able to further elaborate on the risk factors, including genetics, associated with lymphocytic colitis in this environment.

What does this study add to existing knowledge? : This study highlights the fact that lymphocytic colitis may not be as uncommon in sub-Saharan Africa as previously thought. It also shows that lymphocytic colitis in the environment usually have good outcomes when treated with steroids.

Permission from Institutional research board: Yes
Conflict of interest: None
Funding: Nil

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