Epidemiologic and Anatomoclinical Aspects of Ulcerative Colitis in a Referral Center in Cameroon and Review of Literature

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ABSTRACT
Ulcerative colitis was found in 35 out of 356 biopsies of the intestine examined at the pathology unit of the Regional Hospital Buea in Cameroon on endoscopic biopsy specimens referred from a specialized gastrointestinal treatment center in Limbe, South West Region, Cameroon. Files of all patients biopsied from January 1st 2009 to December 31st 2012, a period of 4 years were retrieved and data on both clinical and pathological factors for histologically-confirmed cases of ulcerative colitis were assembled and analyzed. The patients ranged in age from 18 to 77 at a mean of 52 years and a significant female predominance of 57 %. The disease occurred mainly in the 49-69 years age group (81%), with no occupational susceptibility. The lesion was predominantly distal (76%) and presented most often as diarrhea with or without bloody mucoid stools. No extra intestinal symptoms were found. Endoscopy revealed discrete blotchy lesions with loss of surface vascularisation in most cases. Morphologically there was a remarkable absence of pseudopolyps, while microscopy was as described in literature. A routine histology of all colonic biopsies is recommended as this may reveal that ulcerative colitis is not as rare in our setting as previously believed.

Keywords: ulcerative colitis, Crhon’s disease, inflammatory bowel disease. Cameroon

INTRODUCTION
Ulcerative colitis (UC) and Crohn's disease (CD), collectively called inflammatory bowel disease, are disorders of modern society, and their frequency in developed countries has been increasing since the mid-20th century. Ulcerative colitis is the most common form of inflammatory bowel disease worldwide. The gut immune system is generally tolerant of its microbial load, and a breakdown in tolerance is postulated to be central to the pathogenesis of inflammatory bowel disease. Intestinal homeostasis requires a controlled innate immune response to the microbiota, which is recognized by toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)–like receptors on epithelial and immune cells [1]. In contrast to Crohn's disease, ulcerative colitis is a disease of the mucosa that is less prone to complications and can be cured by means of colectomy, and in many patients, its course is mild [2]. It includes characteristic ulcers in the colon and recto sigmoid mucosa, as opposed to CD which may affect any part of the gastrointestinal tract.

The pathogenesis of inflammatory bowel disorders, incriminates both exogenic factors such as infectious agents, normal luminal flora and endogenic factors such as intestinal epithelial cell barrier function, vascular supply and neuronal activity. When the synergy of these factors is altered, the consequence is a
chronic state of deregulated mucosal immune function that is further modified by specific environmental factors like smoking. UC and CD, in the absence of identifiable causative agents are defined empirically by their typical clinical, pathologic, endoscopic, radiologic and laboratory features. These features enable clinicians to distinguish between the two diseases.

Often considered more frequent in western and other developed countries, African countries are considered low prevalence zones because the prevalence of more symptomatic infectious colitides and the absence of diagnostic means make estimation of their prevalence and incidence difficult. The literature on the pathogenesis and treatment of inflammatory bowel disease has tended to focus on Crohn's disease [3-5], and few articles expressly discuss ulcerative colitis [6].

MATERIALS AND METHODS
We studied the files of patients received for colonoscopy from January 2010 to December 2014, a period of 4 years; referred to us and on whom ulcerative colitis was confirmed on histologic biopsy specimens. This study was carried out in Limbe and Buea Regional Hospitals respectively, representing cases referred from the entire South West Region of Cameroon and beyond. The region is predominantly an agro-industrial community and is inhabited majorly by farmers, civil servants, fishermen, clergy, students, traders and persons involved in all types of activities for a living. In this community where diseases of the digestive system have been reported to form about 10% of reasons for medical consultation [7], we decided to find out the epidemiology and and anatomico-clinical aspects of ulcerative colitis in the population.

All patients referred for colonoscopy were re-evaluated, their clinical information was recorded and preparation and informed consent obtained after which colonoscopy was carried out with an Olympus Colonoscope following premedication with parenteral diazepam and hyoscine. All suspicious mucosal lesions were systematically biopsied, fixed in formaldehyde and sent for pathological analysis. For the later, 5 microns diameter sections were made on paraffin wax-embedded specimens, stained with Haematoxyline and Eosine then examined using a light microscope.

RESULTS
35 cases were confirmed with ulcerative colitis and the following observations were made.

![Figure I: Sex distribution](image)

There was a significant (p<0.001) proportion of female compared to male patients.
The disease affects all age groups, but the prevalence is low in the young and elderly. The disease seems to predominate in mid and early elderly age as the age bracket 40-69 years is predominantly affected by 56% of patients.

**Table 1: Occupation of patients with UC.**

<table>
<thead>
<tr>
<th>Profession</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farming</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Civil servants</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Business Men</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Retired</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Students</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>House wives</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Unemployed</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>All occupations</td>
<td>35</td>
<td>100</td>
</tr>
</tbody>
</table>

Professionally active patients were more involved than students, the retired and unemployed. This aspect may be linked to the stress that has been reported to be an etiological factor in UC.

**Table 2: Clinical presentation of patients with UC.**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Number of cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained diarrhoea</td>
<td>25</td>
<td>71.5</td>
</tr>
<tr>
<td>Bloody and mucoid stool</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>Unspecified abdominal pains</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Dyspeptic symptoms</td>
<td>3</td>
<td>8.6</td>
</tr>
<tr>
<td>Total*</td>
<td>63*</td>
<td>180.1*</td>
</tr>
</tbody>
</table>

*Some patients had multiple symptoms
Figure 3: Topographic distribution of lesions

The anus and rectosigmoid are commonest sites of the disease (78%).

Table 3: Endoscopic findings

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>Number</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discrete blotchy lesions with loss of surface vascularisation</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>Extensive erythematous lesions</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Erythematous lesion with friable mucosa</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Superficial ulcero-hemorrhagic lesion</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Pseudopolyposis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cobblestone aspects</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The commonest endoscopic finding in UC are discrete blotchy lesions, erythematous lesions and a friable mucosa.

Figure 3A: cobblestone mucosa

Figure 3B: intense mucosal stromal Inter glandular hemorrhage

Figure 3C: crypt abcess and mucosal inflammation in ulcerative colitis

Figures 3 (A, B, C): morphologic and microscopic aspects of ulcerative colitis
DISCUSSION
Ulcerative colitis is an inflammatory bowel disease sharing much in common with Crohn’s disease. Though it has a worldwide distribution, and more common in the developed world, we believe its diagnoses and clinical presentations are under estimated in favor of parasitic and infection-induced colitides in Cameroon and other developing countries. The incidence of ulcerative colitis is 1.2 to 20.3 cases per 100,000 persons per year, and its prevalence is 7.6 to 246.0 cases per 100,000 per year [8] with highest incidence and in the populations of Northern Europe and North America and the lowest in continental Asia. Of 356 endoscopic biopsies of the gastrointestinal tract analyzed during the 4 years period of this study, 35 were histologically confirmed to be ulcerative colitis, giving a prevalence of about 9.8% or an incidence of 2.5%. From literature, a westernized environment and lifestyle is linked to the appearance of inflammatory bowel disease, which is associated with smoking, diets high in fat and sugar, medication use, stress, and high socioeconomic status [9]. Inflammatory bowel disease has also been associated with appendectomy [9]. Of these factors, only cigarette smoking and appendectomy are reproducibly linked to ulcerative colitis. Removal of an inflamed appendix in early life is associated with a decreased incidence of ulcerative colitis [10].

Studies have suggested that genetic influences play a greater role in Crohn’s disease than in ulcerative colitis [11]. An analysis of some of such studies has confirmed the presence of 47 loci associated with ulcerative colitis, of which 19 are specific for ulcerative colitis and 28 are shared with Crohn's disease [12]. Ulcerative colitis appears to be as genetically heterogeneous as Crohn's disease, but given the large number of implicated genes and the small additive effect of each, genetic screening is not currently indicated to assess the risk of ulcerative colitis. We did not evaluate the possible etiologic factors for the disease amongst our patients.

We found in this study a significant (p<0.001) female predominance of 57% over males 43% (figure 1). The predominance of female patients with digestive organ lesions has been earlier reported in this community [7]. UC can happen at any age, but it usually starts between the ages of 15 and 30 and tends to run in families. Our patients are slightly older with most affected age groups being the 40 -49 and 50-59 years (28% each) (figure II), and present predominantly with pain in the abdomen and blood or pus in diarrhea. Generally the patients presented with unexplained and persistent diarrhea, (87%) bloody mucoid stools (57%), abdominal pain and discomfort (42%) and at times dyspeptic symptoms (table II).

Autoimmunity may play a role in ulcerative colitis. Abnormalities in humoral and cellular adaptive immunity occur in ulcerative colitis. Elevated IgM, IgA, and IgG levels are common in inflammatory bowel disease, but there is a disproportionate increase in IgG1 antibodies in ulcerative colitis [13]. In addition to pANCA, this disease is characterized by circulating IgG1 antibodies against a colonic epithelial antigen that is shared with the skin, eye, joints, and biliary epithelium [14]. This accounts for the extra intestinal symptoms of anemia, severe tiredness, weight loss and loss of appetite, bleeding from the rectum, sores on the skin, joint pain and growth failure in children. Extraintestinal manifestations which may either precede the onset of symptoms or appear and evolve in parallel with intestinal manifestations occur in 10 to 30% of patients with ulcerative colitis. About half of patients have mild symptoms. None of our cases had an extra intestinal manifestation of the disease. There seems to be no occupational predisposition, although housewives (28%), farmers (20%) and businessmen (17%) apparently dominate our findings.

Because inflammation in ulcerative colitis typically does not extend into the small intestine and occurs in proximity to the epithelium, colonocytes are implicated in the pathogenesis of this disease. It has been proposed that the epithelium is diffusely abnormal, irrespective of inflammation [15]. In both ulcerative colitis and Crohn’s disease, epithelial cells have a decreased ability to activate suppressor CD8+ T cells, but this abnormality is probably secondary to other immune events [16]. Extraintestinal manifestations in ulcerative colitis occur because it is possible that cross-reacting antibodies against the colon cause organ-specific damage.

Since barium enemas were not performed due to technical and financial challenges, all our patients had partial or total colonoscopy with targeted biopsy of lesions. Specimens were analyzed and conclusive pathologic diagnosis established. Colonoscopy also enabled us establish a topographic localization of the lesions and classify their severity. Most lesions were found in the distal colon (92%) with predominance in
the rectum and sigmoid colon - the rectosigmoid (56%), rectum and anus (34%) and ascending colon (8%). Lesions extending to the transverse colon (extensive disease) were found in only (8%) of cases (figure 3).

Some endoscopic lesions were discrete and blotchy but with loss of colon vascularisation in 15 cases (42%), extensive and erythematous in 8 (22%), erythematous with friable mucosa (20%) and ulcero-hemorrhagic lesion in (14%) (Table 3). Because inflammation in ulcerative colitis typically does not extend into the small intestine and occurs in proximity to the epithelium, colonocytes are implicated in the pathogenesis of this disease. It has been proposed that the epithelium is diffusely abnormal, irrespective of inflammation [15]. In both ulcerative colitis and Crohn's disease, epithelial cells have a decreased ability to activate suppressor CD8+ T cells, but this abnormality is probably secondary to other immune events [16]. Variants of the XPB1 gene, the product of which is a component of the stress response of the endoplasmic reticulum in epithelial cells, have been linked to inflammatory bowel disease, reinforcing the concept that colonocytes are involved in its pathogenesis [17].

Bloody diarrhoea with or without mucus is the hallmark of ulcerative colitis. The onset is typically gradual, often followed by periods of spontaneous remission and subsequent relapses. Active disease is manifested as mucosal inflammation commencing in the rectum (proctitis) and in some cases spreading to the rest of the colon. Although proctitis is frequently associated with fecal urgency and the passage of fresh blood, constipation may paradoxically occur. Proctosigmoiditis, left-sided colitis, extensive colitis, or pancolitis may lead to diarrhea, frequent evacuations of blood and mucus, urgency or tenesmus, abdominal pain, fever, malaise, and weight loss, depending on the extent and severity of the disease [18]. A small area of inflammation surrounding the appendiceal orifice (cecal patch) can be identified in patients with left-sided ulcerative colitis and in those with proctitis or proctosigmoiditis [19] but this finding is not specific. Similar to these earlier findings, in our series, diarrhea (71.5%) and bloody mucoid stools (57%) were main clinical manifestations (table 2).

In ulcerative colitis, histology shows a typical inflammation which is characteristically restricted to the mucosal layer, with infiltrates varying in density and composition during active disease or stages of remission. Infiltrates consist primarily of lymphocytes, plasma cells, and granulocytes; the last are being particularly prominent during acute flare-ups and accumulate in crypt abscesses [20]. Other typical features include goblet-cell depletion, distorted crypt architecture, diminished crypt density, and ulcerations. Our findings on histology were similar to these reports (see figure 3B and C). However, epithelioid granulomas, which are typical of Crohn's disease, are not present. Looking for epithelial dysplasia is critical, given the risk of cancer in patients with long-standing ulcerative colitis; however, dysplasia can occur at any stage without indicating malignant transformation. There are no exact criteria for the diagnosis of ulcerative colitis, but in most cases, the presence of two or three of the aforementioned histologic features will suffice [21].

The severity of inflammation on histologic examination and the severity of disease on endoscopic examination may not coincide; for instance, histologic findings may indicate severe disease even in a patient with endoscopically quiescent disease. Although no diagnostic, laboratory measurements are helpful in assessing and monitoring disease activity and in differentiating ulcerative colitis from other forms of colitis. Blood counts and measurements of the erythrocyte sedimentation rate and the level of fecal lactoferrin or calprotectin help determine the severity of the inflammation. Stool cultures for Clostridium difficile, campylobacter species, and Escherichia coli are recommended to rule out an infectious cause or complication. Patients with severe, refractory disease should be assessed for cytomegalovirus infection by means of histologic, immunochemical, serologic, culture, or DNA testing [22].

According to current consensus-based guidelines, the choice of treatment for patients with ulcerative colitis should take into consideration the level of clinical activity (mild, moderate, or severe) combined with the extent of disease (proctitis, left-sided disease, extensive disease, or pancolitis), the course of the disease during follow-up, and patients' preferences [23, 24]. The prognosis for patients with ulcerative colitis is generally good during the first decade after diagnosis, with a low rate of colectomy; over time, remission occurs in most patients [2 Solberg]. In our series, there were no extra-digestive manifestations, and further laboratory and radiologic workup was not initiated. The patients were subsequently placed on empirical treatment and followed up.
Acute complications, such as severe bleeding and toxic megacolon, may occur in patients with extensive or severe inflammation; other problems, such as epithelial dysplasia or cancer, may emerge during the chronic phase. On the basis of data from referral centers, the cumulative risk of colorectal cancer among patients with chronic ulcerative colitis may reach 20 to 30% at 30 years [25], but the incidence rate is much lower in population-based series (approximately 2%) [26]. Risk factors for cancer include a long duration of disease, regardless of clinical activity; extensive involvement; a young age at onset; severe inflammation; the presence of primary sclerosing cholangitis; and a family history of colorectal cancer. Although surveillance colonoscopy is recommended for patients at risk, there is no clear evidence that such surveillance increases survival [27]. We are still following up our patients for possible complications.

CONCLUSION
UC is becoming a more frequent finding in our environment. It is predominant at middle age in both sexes and affects patients of all works of life, with an ano-recto-sigmoid predilection. Adequate clinical and endoscopic evaluation needs to be carried out and biopsies done to confirm the diagnosis. The clinical signs of the disease and histology are similar to that reported in literature, with exceptional absence of pseudopolyps and cobblestone on histology. Assessment of the clinical activity of ulcerative colitis helps the clinician choose diagnostic tests and make therapeutic decisions. Various indexes of disease activity have been developed on the basis of clinical, laboratory, and endoscopic findings. Unfortunately most cases in our environment are considered as non specific or parasitic colitides and treated without any further investigations. The authors recommend colonoscopy for all patients presenting with chronic diarrhea, blood stained stools, persistent abdominal discomfort and pain to rule in/out an ulcerative colitis and further in-depth studies to document incidence and trends of the disease in our community.

REFERENCES

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