Clinical Characteristics of Crohn's Disease in a Cohort from Saudi Arabia

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Abstract

Objective: In Saudi Arabia, there are limited studies on the clinical characteristics of patients specifically with Crohn's disease (CD). This study was conducted to describe the clinical characteristics of CD at a tertiary care center in Jeddah, Saudi Arabia.

Methods: This retrospective study included all patients aged >14 years who had a definitive diagnosis of CD and were managed at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between 2012 and 2018. Data were collected for the following categories: clinical, laboratory, radiological, histological features at presentation, and disease-related complications.

Results: The study included 245 newly diagnosed CD patients, aged 14–73 years (median: 26.3 years). All subjects presented with abdominal pain. Majority of the patients (59.7%) received a definitive diagnosis of CD >3 months after the onset of symptoms; 15.1% were initially suspected to have intestinal tuberculosis. Diarrhea and bleeding per rectum were reported in 60.8% and 49.7% of the patients, respectively. Sacroiliitis was the most frequent extraintestinal manifestations (11.4%). In terms of disease location, the terminal ileum (L1) was the most affected area (46.9%). Twenty-five patients had perianal disease, of which 40% had complex fistulae and 36% had perianal abscesses. The majority had hemoglobin levels >10 g/dl (74.1%), decreased serum iron (69.6%) and ferritin (50.5%) levels, and elevated erythrocyte sedimentation rate (68.2%) and C-reactive protein (82.2%).

Conclusions: The majority of the patients in our cohort presented with the characteristic quartet of abdominal pain, weight loss, fever, and diarrhea. This study also found a significant number of patients with CD in Saudi Arabia experience diagnostic delay, which may contribute to disease morbidity and complications. These findings highlight the need for future studies to determine factors influencing this diagnostic delay.

Keywords: Crohn's diagnosis, Crohn's disease, diagnostic delay, gastrointestinal diseases, inflammatory bowel disease, Saudi Arabia

INTRODUCTION

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) that causes chronic granulomatous inflammation of the gastrointestinal tract. It has a high recurrence rate and unpredictable disease course. Recent studies have shown an increased global trend in the prevalence of CD in Western countries,[1-4] Asia,[5,6] and the Arab world.[7] The incidence of CD is also increasing in Saudi Arabia.[8-11]

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The disease is characterized by transmural inflammation, which may result in strictures, micro-perforations, and fistulae. Inflammation of the intestinal wall is not necessarily continuous, and thus, CD has a characteristic "skip lesions," in which the disease is observed intermittently throughout the bowel. Histologically, CD displays transmural lymphoid aggregates, fissuring, non-necrotizing granulomas, and microscopic skip lesions. While granulomas are strongly suggestive of CD, they occur only in 40–60% of the CD patients.

CD may initially manifest as recurrent abdominal pain or diarrhea, symptoms often mistaken for irritable bowel syndrome (IBS) in clinical practice. The symptoms of CD may be present for several months or years prior to diagnosis and the initiation of treatment. A recent study from central Saudi Arabia found that the average duration between the onset of symptoms and diagnosis was 11 months.[10] Many factors were reported to result in delay in CD diagnosis including patient and physician-related factors such as a delay in seeking medical care secondary to patient ignorance, psycho-social or cultural beliefs, inadequate clinical evaluation, and insufficient follow-up.[12] According to several reports from Saudi Arabia,[8,10,13,14] abdominal pain, diarrhea, and weight loss are the most common presenting symptoms in patients with CD. Extraintestinal manifestations such as arthralgia, clubbing of the fingers, and pallor have also been documented.[8,10,13,14] Rare extraintestinal manifestations include ocular manifestations and sclerosing cholangitis, which are observed in <5% of the patients. Data from Saudi Arabia also support an increased risk of CD in relatives of patients with IBD.[15,16]

There are conflicting results among national and international studies with regards to the median age at diagnosis, symptom duration prior to diagnosis, and gender preponderance in CD. Further, in Saudi Arabia, there are limited studies on the clinical characteristics of patients specifically with CD. An improved understanding of the clinical characteristics and complications of CD would provide a more robust context for evaluating future intervention-based research. This study was conducted with the objective of describing the clinical characteristics of CD in a university hospital from the Western region of Saudi Arabia.

METHODS

Study design, setting, and participants
This retrospective study included all patients aged >14 years who had a definitive diagnosis of CD and were managed at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between 2012 and 2018. Patients were considered to have "definite" CD when they fulfilled a combination of clinical, endoscopic and histologic criteria, based on the World Health Organization's diagnostic criteria for Crohn's disease.[17] The study was conducted after obtaining approval from the Research Ethics Committee of King Abdulaziz University, Jeddah, Saudi Arabia.

King Abdulaziz University Hospital is one of the largest tertiary care government hospitals in the western region of Saudi Arabia and receives patients from across the country. Therefore, the patients from this hospital can be adequately representative of the population.

Data collection
Patient data were collected from the electronic database of the hospital. The study aimed at reporting the most common clinical, laboratory, radiological, and histological features associated with CD. Accordingly, data on demographic variables (age, gender, nationality, and residence location in Saudi Arabia), clinical variables (clinical presentation, symptoms, symptom duration, time interval between the onset of symptoms and diagnosis, extraintestinal manifestations, number of previous hospital admissions, past medical history, past surgical history, and family history), diagnosing physician's specialty, and treatment offered were collected. In addition, data on laboratory findings (complete blood count, erythrocyte sedimentation rate, C-reactive protein, iron level, total iron binding capacity, ferritin level, and stool analysis) were also extracted, and imaging reports including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen and perianal area were reviewed. Endoscopy and histopathological results were also reviewed.

Scoring and categorization
The electronic records did not include unified scores for evaluation of disease activity or severity. However, we categorized the different collected items according to the various reported scores for CD's activity and severity.[18] Abdominal pain, bowel frequency, presence of abdominal mass and presence of extraintestinal manifestations were categorized into the Harvey–Bradshaw index.[19] Presence of blood in stool was classified into trace, occasionally frank, and usually frank, according to the Clinical Scoring System for the Simple Clinical Colitis Activity Index.[20] Laboratory tests were categorized according to Truelove and Witts' disease activity grades in inflammatory bowel disease.[21] The location and extension of bowel segments involved were classified according to the Montreal Classification of Inflammatory Bowel Disease: terminal ileal, L1; colonic,

L2; ileocolonic, L3; and upper gastrointestinal (GI), L4.[22] Perianal fistulizing disease was recorded as a modifier of the disease behavior (p), and the fistulas observed on MRI were classified as simple or complex, according to the Perianal Crohn's Disease Activity Index.[23]

Statistical analysis
Data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL, US). Descriptive statistics were computed for all variables. Results are expressed as frequency (percentage) for categorical variables and as mean (standard deviation [SD]) and range for continuous variables.

RESULTS

A total of 245 patients newly diagnosed with CD met the inclusion criteria of the study. Patients' age ranged from 14 to 73 years (median age: 26.3 years). About half of the sample (51%) were males, and 68.5% were Saudi [Table 1].

Diagnosis
Most patients (59.7%) received a definitive diagnosis of CD only >3 months after the onset of symptoms. About 15.1% (n = 37) of the patients were initially suspected to have intestinal tuberculosis, which contributed to delay in the diagnosis; none received antitubercular medication, as definite diagnosis was not reached.[24] The majority of the participants (71.4%) were diagnosed by gastroenterologists, while only 3.5% were diagnosed by general practitioners [Table 2].

Clinical presentation
All participants presented with abdominal pain: central abdominal pain (45.5%) was the most common, followed by the right and left lower quadrants (34.0% and 8.4%, respectively). About 65% reported their abdominal pain intensity as "severe." Diarrhea was documented in 60.8% of the participants, while the remaining had regular bowel habits. Among those who reported diarrhea, 2.9% experienced alternating bouts of constipation and diarrhea. About half of the patients (49.7%) reported blood in stool; bloody stools were predominant in 23.8%. Weight loss, fever, and vomiting (46.1%, 38.8%, and 38.8%, respectively) were other common presenting symptoms. Of those with weight loss, 19.5% had lost >10% of their body weight at presentation [Table 3].

Extraintestinal manifestations
Sacroiliitis was the most frequent extraintestinal manifestation (11.4%), followed by arthritis or arthralgia (6.5%) and aphthous ulcers of the oral cavity (4.9%). Scleritis, erythema nodosum, and deep

Table 1: Demographic characteristics of the sample

Variables	n (%)
Gender	
Male	125 (51)
Female	120 (49)
Nationality (n=235)	
Saudi	161 (68.5)
Non-Saudi	74 (31.5)
Origin, if Saudi (n=62)	
Central region	5 (8.1)
Southern region	11 (17.7)
Western region	46 (74.2)

Table 2: Diagnosis and admissions

Variables	Frequency
Time from symptom onset to diagnosis (months) (n=233)	
<1	44 (18.9)
1-3	50 (21.5)
>3	139 (59.7)
Diagnosis made by (n=231)	
General practitioner	8 (3.5)
Internist	41 (17.7)
Gastroenterologist	165 (71.4)
Surgeon	17 (7.4)
Number of admissions (n=244)	
None	56 (23.0)
1	43 (17.6)
2-3	61 (25.0)
>3	84 (34.4)

venous thrombosis were infrequent extraintestinal manifestations [Table 3].

Medical and surgical history
About 10.2% of the participants had a history of perianal disease, 4.5% of tuberculosis, and 4.1% of contact with an individual diagnosed with tuberculosis. Upper gastrointestinal tract involvement was reported in 4.9% of the patients. Ten patients (4.1%) had a family history of CD and 3 (1.2%) of tuberculosis. Twenty-eight patients underwent bowel surgery (11.4%), either prior to or following CD diagnosis, with right hemicolectomy accounting for three-fourths of all surgeries. The majority were admitted to a hospital at least three times during the illness [Table 4].

Imaging findings
Seventy-nine patients (32.2%) had an ultrasound examination. Findings were suggestive of a thickened bowel (20.3%), intra-abdominal or pelvic collections (16.5%), and an abdominal mass (3.8%). Ultrasound revealed enlarged lymph nodes in 10 patients, of which 60% had >1 cm in diameter [Table 5].

A computed tomography (CT) examination was performed in 123 patients. Findings included abdominal collections (17.9%), abdominal masses (11.4%), and thickened bowel (62.6%). CT revealed enlarged lymph nodes in 61 of 123 abdominal CT examinations (49.6%), the

majority of which were <1 cm in diameter (62.3%) [Table 5]. Based on the Montreal classification for disease location, the terminal ileum (L1) was the most affected area (115 patients; 46.9%) followed by the ileocolonic area (L3) (106 patients; 43.3%) [Table 6]. Twenty-five patients had perianal disease, of which complex fistulae were noted in 10 cases (40%) [Table 5].

Laboratory and histopathology findings

Histopathological examination was available in only 126 (51.4%) of the patients' records, and revealed non-caseating granulomas in 23 (18.2%). Acid-fast bacilli were isolated in only 2 (1.5%) patients. Thirty-five patients underwent polymerase chain reaction to diagnoses tuberculosis, resulting in 3 positive tests (8.5%); that is, three patients had both TB and CD simultaneously [Table 6].

White blood cell counts, platelets, and total iron binding capacity were normal in most patients [Table 7], and the majority (74.1%) had hemoglobin levels >10 g/dl. Serum iron and ferritin were below normal levels in 69.6% and

Table 3: Clinical presentations and symptoms of the patients

Variables	n (%)	Percent
Abdominal pain at presentation (n=224)		
Mild	78 (34.8)	34.8
Severe	146 (65.2)	65.2
Location of abdominal pain at presentation (n=191)		
Right lower quadrant	65	34.0
Left lower quadrant	16	8.4
Central	87	45.5
Diffuse	19	9.9
Right lower and left lower quadrants	4	2.1
Abdominal distension at presentation	40	16.3
Nausea at presentation	63	25.7
Vomiting at presentation	95	38.8
Fever at presentation	95	38.8
Excessive night sweating	13	5.3
Weight loss	113	46.1
Degree of weight loss (n=113)		
<10%	91	80.5
>10%	22	19.5
Bowel habit (n=245)		
None	78	31.8
Constipation	11	4.5
Diarrhoea	149	60.8
Diarrhoea and constipation	7	2.9
Frequency of diarrhoea (times/day) (n=144)		
<4	94	65.3
4–6	35	24.3
>6	15	10.4
Characteristics of diarrhoea (n=147)		
Usually frank blood	35	23.8
Occasionally frank blood	39	26.5
Trace of blood	73	49.7
Extraintestinal symptoms (n=245)		
Arthritis	16	6.5
Sacroiliitis or back pain	28	11.4
Erythema nodosum	3	1.2
Scleritis (painful eyes)	5	2.0
Aphthous ulceration	12	4.9
Deep venous thrombosis	2	0.8

Table 4: Patients' medical and surgical histories

Variables	Frequency (%)
Family history of Crohn's disease	10 (4.1)
Perianal disease	25 (10.2)
Other percutaneous fistulae	6 (2.4)
Upper gastrointestinal involvement	12 (4.9)
Personal history of tuberculosis	11 (4.5)
Family history of tuberculosis	3 (1.2)
Contact with tuberculosis patient	10 (4.1)
Previous bowel surgeries	28 (11.4)
Type of surgery	
Proctectomy	1 (3.7)
Colostomy	1 (3.7)
Ileostomy	3 (11.1)
Right hemicolectomy	20 (74.1)
Small bowel resection	2 (7.4)

Table 5: Radiology investigations

Variables	Frequency (%)
Ultrasound abdomen and pelvis	79 (32.2)
Lymph node observed on ultrasound (cm) (n=10)	
<1	4 (40.0)
>1	6 (60.0)
Collections observed on ultrasound	13 (16.5)
Mass observed on ultrasound	3 (3.8)
CT (n=183)	
No	58 (31.7)
CT abdomen and pelvis + enterography	123 (67.2)
Magnetic resonance enterography	2 (1.1)
Lymph node observed on CT (n=68)	
Few	30 (44.1)
Many	38 (55.9)
Lymph node size (cm) (n=61)	
<1	38 (62.3)
>1	23 (37.7)
Collection observed on CT	22 (17.9)
Mass observed on CT	14 (11.4)
Thick bowel wall observed on CT	77 (62.6)
Large bowel involvement observed on CT	45 (36.6)
Small bowel involvement observed on CT	89 (72.3)
Small and large bowel involvement on CT	29 (23.6)
Terminal ileum involved	48 (39.0)
Proximal areas	8 (6.5)
Areas of involvement in the small bowel (n=59)	
Multiple	12 (20.3)
Single	47 (79.7)
MRI of the perianal area	25 (10.2)
Simple fistula	15 (60)
Complex fistula	10 (40)
Presence of a collection on MRI	9 (28.1)

CT: Computed tomography, MRI: Magnetic resonance imaging

Table 6: Histopathological and endoscopic examinations

Variables	n (%)
Histological findings of colonic biopsy	126 (51.4)
Noncaseating granuloma on histological examination	23 (18.2)
Acid-fast bacilli	2 (1.5)
PCR for tuberculosis	35 (27.8)
Positive PCR for tuberculosis	3 (8.5)
Gastrointestinal location on endoscopy (according to Montreal classification)	
Colonic (L2)	24 (9.8)
Illeocolonic (L3)	106 (43.3)
Terminal ileum (L1)	115 (46.9)
Proximal bowel involvement (L4)	8 (3.3)

PCR: Polymerase chain reaction

Table 7: Laboratory investigations

Variables	Frequency
White blood cell count (*n*=231)	
Low	14 (6.1)
Elevated	44 (19.0)
Normal	173 (74.9)
Platelet count (*n*=23)	
Low	5 (2.2)
Elevated	41 (17.8)
Normal	184 (80.0)
Haemoglobin level (*n*=228) (g/dl)	
>10	169 (74.1)
<10	59 (25.9)
Serum iron (*n*=115)	
Normal	35 (30.4)
Low	80 (69.6)
Serum ferritin (*n*=111)	
Normal	46 (41.4)
Low	56 (50.5)
High	9 (8.1)
Total iron binding capacity (*n*=83)	
Low	12 (14.5)
Normal	48 (57.8)
High	23 (27.7)
Erythrocyte sedimentation rate (*n*=211)	
Normal	67 (31.8)
High	144 (68.2)
C-reactive protein (*n*=213)	
Normal	38 (17.8)
High	175 (82.2)
C-reactive protein level (*n*=164)	
<20	101 (61.6)
20-40	29 (17.7)
>40	34 (20.7)
Pus cells observed on stool examination (*n*=165)	
Yes	23 (13.9)
Entamoeba histolytica observed on stool examination (*n*=132)	
Yes	7 (5.3)

50.5% of the patients, respectively. Most of the cohort had an elevated erythrocyte sedimentation rate (68.2%) and C-reactive protein (82.2%). Stool analysis revealed pustular cells (i.e., white blood cells/neutrophils) in 23 patients (13.9%) and *Entamoeba histolytica* cysts in seven patients (5.3%).

DISCUSSION

This descriptive study of patients newly diagnosed with CD at a university hospital in the Western region of Saudi Arabia documents three important findings: a significant diagnostic delay, the characteristic presenting symptoms, and radiological findings.

Diagnostic delay was frequent in the cohort. Our findings are consistent with previous hospital-based studies conducted in Western[25-27] and Gulf[28-30] countries. We hypothesize that in our cohort, this delay was secondary to patient characteristics, such as delay in the patients seeking initial medical advice, and practitioner characteristics, such as not considering CD at the initial medical evaluation.

Some authors have also found that diagnostic delay may be affected by patient's socioeconomic status.[31,32] However, findings from a prospective study conducted at two referral centers in France did not find any significant correlation between socioeconomic status and diagnostic delay.[26] In the current study, other patient demographical factors did not influence diagnostic delay in CD. As our study design precludes determination of causality, future studies are needed to unequivocally determine factors that influence the diagnostic delay in CD patients.

The prevalence of isolated small bowel disease in the current study is relatively higher (46%) compared with other studies in the literature.[33] This high percentage could be due to referral bias, as the data collected are from a large tertiary care referral center for IBD. The majority of the patients in our cohort presented with the characteristic quartet of abdominal pain, weight loss, fever, and diarrhea. These four symptoms have previously been reported in the medical literature as the hallmark symptoms of CD.[34] While the majority of patients in our study presented with diarrhea (60.8%), it was less prevalent than that reported in other studies (70–90%).[35-37] Our findings are consistent with the "red flag" signs and symptoms suggestive of a diagnosis of CD, as reported by Danese *et al.*[38] The findings from our study indicate the need to educate general practitioners about these red flags to improve the frequency of early diagnosis.

Extraintestinal symptoms were not uncommon in our cohort: approximately one-fifth of the participants reported sacroiliitis or back pain. Joint involvement is the most prevalent extraintestinal manifestations observed in our study, which is different from the data reported in the literature. For example, Card *et al.*,[39] reported skin manifestations such as pyoderma gangrenosum and erythema nodosum were the most common extraintestinal symptoms. As the extraintestinal symptoms in CD often overlap with those of other IBD conditions, diagnosis may be even more challenging in this subset population.[40] The radiologic and endoscopic findings in our patients are similar to that of patients in studies conducted nationally and internationally.

Limitations
The current study has limitations such as its small sample size and retrospective design, and thus, the results should be interpreted with caution. Importantly, data regarding follow-up, change in disease behavior, number of flares, types of therapy, and patient outcomes could not be evaluated. Another limitation was that a unified score for evaluation of the disease severity and activity was not used

among the patients, although most cases were diagnosed by gastroenterologists.

CONCLUSIONS

A significant proportion of CD patients in the study cohort experienced diagnostic delay, which may have contributed to disease morbidity. The finding highlights the need for future studies to determine factors that influence diagnostic delay in patients with CD in the region, as well as the need for educating general practitioners for an early diagnosis of CD.

Ethical considerations

The study received ethical approval from the Research Ethics Committee at King Abdulaziz University (Ref. no.: 51-15; date: March 09, 2015). Requirement for consent was waived by the Ethics Committee owing to the study design. The study adhered to the principles of the Declaration of Helsinki, as revised in 2013.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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