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Association of Inflammatory Pathologies and Crohn's Disease: A Retrospective Study in the West Algerian Region

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ABSTRACT

Background: Crohn's disease is a chronic and recurrent inflammatory bowel disease that progresses slowly. Also CD patients have a large number of extra-intestinal manifestations.

Objective: we sought to define the possible associations between inflammatory pathology and localization and on the other hand, inflammatory pathologies and the disease behavior

Methods: A retrospective analytical study was carried out at the level of gastric and general surgery services of Western Algerian University Hospital of Sidi Bel Abbes region, during the period 2007-2019.

Results Our study was based on a total sample of 295 cases involving 114 females (38.6%) and 181 males (61.4%) with a sex ratio of (1.58). The location of the disease at the time of diagnosis was dominated by the ileo-caecal location (55.3%), of which 64.4% were associated with inflammatory pathology (IP). The majority of patients diagnosed with Crohn's disease had an inflammatory behavior and this for all age groups. The appendix, the ulcer and inflammatory anemia are most associated with Crohn's disease. For inflammatory extra-intestinal manifestations, only group of patients with arthralgia had significantly higher rates in the 20-60 age groups. The mainly noted risk factors were appendectomy with (17.3%), smoking (22.4%) with a highly significant association, and alcoholism (6.1%).

Conclusion According to our results the association of inflammatory pathology and crohn disease is more frequent in male and dominated by arthralgia as extra-intestinal manifestations lesions.

Keywords: Crohn disease; Inflammatory pathology; disease behavior; inflammatory extra-intestinal manifestation.

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INTRODUCTION:

Crohn's disease (CD) is a chronic and recurrent inflammatory bowel disease that progresses slowly and is characterized by an inflammatory exacerbation and regression [1,2].

Patients may develop one or more phenotypes during the course of their disease, and often progress from inflammatory disease to severe complications. Unfortunately, there is no cure for CD and most patients need at least one surgical resection [3].

In addition, patients suffering from other gastrointestinal diseases may also have a large number of extra-intestinal manifestations, the main symptoms of which affect the musculoskeletal system. It is hypothesized that lymphocytes activated in the gut migrate to the joints and trigger the

onset of extraintestinal manifestations in the joints [4]. Other groups of inflammatory pathologies, such as inflammatory anemia, peritonitis, ulcer, villous atrophy and appendicitis are seen in Crohn's disease. These latter can occur before the actual bowel disease is diagnosed.

Certain risk factors such as tobacco, infection, pharmacological agents, stress, pollution and diet have been the most incriminated causes of these pathologies [5]. However, some studies in the development of CD are contradictory, as some have found that appendectomy has a role in the onset and clinical course of the disease, while others have shown that there is no association between appendectomy and the development of CD [6].

In this study, we sought to define the possible associations between inflammatory pathology and localization and on the other hand, inflammatory pathologies and the disease behavior. We also investigated whether one of the inflammatory pathologies was more likely to be associated with Crohn's disease.

PATIENTS AND METHODS:

It was an analytical retrospective study including 295 patients diagnosed with Crohn's disease at the level of gastrology and general surgery services of Western Algerian University Hospital "Dr. Hassani Abdelkader" of Sidi Bel region, during the period 2007-2019.

The data collection was carried out using medical records including the following medical features: age, sex, location, disease behavior, treatment, inflammatory pathologies and risk factors.

Statistical analysis:

The statistical analytical study and raw data were processed using rates and cross-tabulations. Associations between categorical parameters were tested using the Chi-square test ($\chi 2$). The results were presented using the p-value, the level of its significance was limited by the 5% rate. All data were processed and analyzed by SPSS 20.0 (Statistical Package for the Social Sciences, IBM Corporation, Chicago, IL August 2011).

RESULTS:

Our study was based on a total sample of 295 cases involving 114 females (38.6%) and 181 males (61.4%) with a sex ratio of (1.58). The age range was between 16-80 years, which represents an average of 38.91. Most of the patients were in the age group of 20-40 years (138/74) M/F. We found a significant association of 0.02 between inflammatory pathology (IP) and Crohn's disease with a percentage of 12.8% of females and 31.9% of males (Tables 1 and 2).

The location of the disease at the time of diagnosis was dominated by the ileo-caecal location 55.3% and present in all age group. 64.4% of them were associated with IP and with a significant association (SA) of 0.004. The colonic localization detected in the age groups <20-80 years (37.6%), of which 28% were associated with IPs and with an AS of 0.003. Finally, the jejunal localization with a percentage of 7.1% was only present in the age groups 20-80 years, and only 7.6% of them were associated with IPs (Tables 1, 2).

The majority of patients diagnosed with Crohn's disease had an inflammatory behavior (46.8%) and this for all age groups. 50.8% of them was associated with inflammatory pathologies (Tables 1, 2). Similarly, common studied population complained of occlusive syndrome (36.9%), sub-occlusive syndrome (23.4%), fistula (12.9%), and (6.4%) abscess and perineal Sd (Tables 1).

We also point out that the disease can be diagnosed by biological examination and para-clinical examination.

Biological examination showed that 34.2% of men had anemia (<130g/l), however, 24.7% of women had anemia (<120g/l). The inflammatory assessment based on CRP and Vs showed that 37.3% of patients had CRP (>11mg/l) and 38% had Vs 1h (>7mm); 2h (>11mm). Serology assessment showed that 02% had ASCA positive, 1.7% EBV positive, 7.1% TB positive, 1.7% Cytomegalovirus, 6.8% ECB and 0.7% had Varicella zoster virus (Table 1).

The para-clinical examination study showed that 60.7% were examined by ultrasound, 59.7% hail transit, 44.7% scan, 38% radiography, 36.3% telethorax, 33.2% barium enema and 5.8% PSA. Other patients underwent endoscopic examination including 79% colonoscopy and 26.1% rectosigmoidoscopy (Table 1).

Crohn's disease treatment is medical and often surgical, indeed, 24.1% are treated with 5-asa, of which 34.8% of its patients take 5-asa treatment combined with PIs with a highly significant association of <0.0001. 13.6% of patients were treated with immunosuppressants. 6.4%, patients treated with corticosteroids and biotherapy. Only 6.1% of patients receiving biotherapy associated with IP (Table 1,3).

Sometimes, surgical treatment becomes necessary since 29.2% of patients underwent ileocaecal resection with ileocolic anastomosis, 13.9% right hemi-colectomy, 13.6% ileal resection with ileo-leal anastomosis, 10.5% sigmoid resection, 5.1% jejunal resection and fistula resection and finally 1.4% total coloprotectomy (Table 1).

With regard to the association of Crohn's disease and inflammatory pathologies, two groups have been identified that do not differ significantly with age groups, namely (Tables 1, 3) :

- 7.1% have peritonitis,
- 2.4% have gastritis,
- 1.7% have ulcerativecolitis,
- 0.7% have villous atrophy and chronic bronchopneumopathy,
- - 0.3% have meningitis.

And those that have a significant association with the age groups:

- 33.3% have the appendix at a significant rate (p=0.01) in the under-20 age group, however it was 66.7% in the 20-40 age group.
- The ulcer appeared with a rate of 33.3% (p=0.02) in the under-20age group. It increased to 66.7% in the 20-40 age group.
- 66.7% for inflammatory anemia was reported in patients with disease started less than 20 years with a highly significant rate (p= <0.001).

For inflammatory extra-intestinal manifestations, we noted that only the group of patients with arthralgia (12.5%) had significantly higher rates in the 20-40 (p=0.01) and 40-60 (p=0.02) age groups; however, Ankylosing spondylitis had a rate of 7.5% and arthritis a rate of 2.4% (Tables 1, 3).

We reported as well that all patients who suffered only from Crohn's disease had significant rates in the 20-40 year age

group (p = 0.004), 40-60 year age group (p = 0.004) and 60-80 years (p = 0.05).

The major noted risk factors were: appendectomy with (17.3%), smoking 22.4% with a highly significant association p= <0.0001 of which 26.5% are associated with IP, and the last risk factor was alcoholism 6.1% with p=0.001, of which 6.8% are associated with IP (Tables 1, 2).

Table 01 : Patients medical features

Characteristics :	**Number of cases**	**Percentage %**
Gender		
Female	114	38.6
male	181	61.4
Age range		
>20 years	14	4.7
20-40 years	212	71.9
40-60 years	55	18.6
60-80 years	14	4.7
minimum age	16 years old	mean age 38.91
maximum age	80 years old	**Standard deviations** 14.7
Age range at presentation		
>20 years	23	7.8
20-40 years	223	75.6
40-60 years	42	14.2
60-80 years	7	2.4
minimum age at presentation	12 years	
Location		
Ileo-caecal location	163	55.3
Colonic location	111	37.6
Jejunal location	21	7.1
Behavior		
Inflammatory.T	138	46.8
Stenosing.T	126	42.7
Fistula.T	24	8.1
ano-perineal.T	7	2.4
Clinical feature		
Pain syndrome	19	6.4
Occlusive syndrome	109	36.9
Sub-occlusive syndrome	69	23.4
Crohn disease	27	9.2
Fistula	38	12.9
Abscess	19	6.4
Perineal syndrome	14	4.7
Biological examination		
CRP (>11mg/l)	110	37.3
Vs 1h (>7mm) ; 2h (>11mm)	112	38.0

Anemia		
male<130g/l	101	34.2
Female<120g/l	73	24.7
Serology		
ASCA	6	2.0
ANCA		
Negative	2	0.7
Not done	293	99.3
EBV	5	1.7
TB	21	7.1
ECB	20	6.8
Cytomegalovirus	5	1.7
Varicelle zona virus	2	0.7
Para-clinical examination		
PSA	17	5.8
Telethorax	107	36.3
Radiography	112	38.0
Barium enema	98	33.2
hail transit	176	59.7
Uultrasound	179	60.7
Scan	132	44.7
Colonoscopy	233	79
Rectosigmoidoscopy	77	26.1
Fibroscopy	29	9.8
Treatment		
5-asa	71	24.1
Immunosuppressants	40	13.6
Corticosteroids	19	6.4
Biotherapy	19	6.4
Operating indications		
Total coloprotectomy	04	1.4
Right hemi-colectomy	41	13.9
Fistula resection	15	5.1
Ileal resection with ileo-leal anastomosis	40	13.6
Ileocaecal resection with ileocolic anastomosis	86	29.2
Sigmoid resection	31	10.5
Jejunal resection	15	5.1
Not done	63	21.4
Inflammatory pathology	132	44.7
Appendix	03	1.0
Villous atrophy	02	0.7
Ulcer	03	1.0
Chronicbronchopneumopathy	02	0.7

Meningitis	01	0.3
Ulcerative colitis	05	1.7
Crohn disease	90	30.5
Inflammatory anemia	03	1.0
Gastritis	07	2.4
Peritonitis	21	7.1
Extraintestinal manifestations « inflammatory »		
Ankylosing spondylitis	22	7.5
Arthralgia	37	12.5
Arthritis	07	2.4
Risk factors		
Appendectomy	51	17.3
smoking	66	22.4
Alcoholism	18	6.1

Table 02: Association with inflammatory pathology and medical features.

	Associated with inflammatory pathology N (%)	**Not associated with inflammatory pathology** N (%)	**P-Value**
Gender (F/M)	38/94 **(28.8/71.2)**	76/87 (46.6/53.4)	**0.002**
Location			
Colonic localization	37 (28)	73 (44.8)	**0.003**
Ileo-caecal location	85 (64.4)	78 (47.9)	**0.004**
Jejunal localization	10 (7.6)	11 (6.7)	0.78
Behavior			
Inflammatory.T	67 (50.8)	71 (43.6)	0.21
Stenosing.T	52 (39.4)	73 (44.8)	0.35
Fistula.T	08 (6.1)	16 (9.8)	0.24
ano-perineal.T	04 (03)	03 (1.8)	0.50
Treatment			
5-asa	46 (34.8)	25 (15.3)	**<0.0001**
Immunosuppressants	18 (13.6)	22 (13.5)	0.97
Corticosteroids	05 (3.8)	14 (8.6)	0.09
Biotherapy	08 (6.1)	11 (6.7)	0.81
Smoking	35 (26.5)	31 (19)	0.12
Alcoholism	09 (6.8)	09 (5.5)	0.64

Table 03 : Cumulative extraintestinal manifestations and complications in Crohn's disease

Characteristics :	>20	20-40	40-60	60-80
Extraintestinal manifestations « inflammatory » *« n (%)p »*				
Ankylosing spondylitis	01**(4.5%)** p=0.9	18**(81.8%)** p=0.2	02**(9.1%)** p=0.2	01**(4.5%)** p=0.9
Arthralgia	01**(2.7%)** p=0.53	33**(89.2%)** p=0.01	02**(5.4%)** p=0.02	01**(2.7%)** p=0.53
Arthritis	00 **(00)** p=0.5	06 **(85.7%)** p=0.4	01 **(14.3%)** p=0.7	00 **(00)** p=0.5
Inflammatory pathology« n (%) p »				
Appendix	01 **(33.3%)**p=0.02	02 **(66.7%)** p=0.8	00 **(00)** p=0.4	00 **(00)** p=0.6
Villous atrophy	00 **(00)** p=0.7	02 **(100%)** p=0.3	00 **(00)** p=0.5	00 **(00)** p=0.7
Ulcer	01 **(33.3%)**p=0.02	02 **(66.7%)** p=0.8	00 **(00)** p=0.4	00 **(00)** p=0.6
Chronic bronchopneumopathy	00 **(00)** p=0.7	01 **(50%)** p=0.4	01 **(50%)** p=0.2	00 **(00)** p=0.7
Meningitis	00 **(00)** p=0.8	01 **(100%)** p=0.5	00 **(00)** p=0.6	00 **(00)** p=0.8
Ulcerative colitis	00 **(00)** p=0.6	05 **(100%)** p=0.1	00 **(00)** p=0.2	00 **(00)** p=0.6
Crohn disease	06 (6.7%) p=0.3	75 (83.3%) p=0.004	08 **(8.9%)**p=0.004	01 **(1.1%)**p=0.05
Inflammatory anemia	02 **(66.7%**) p=<0.0001	00 **(00)**p=0.005	01 **(33.3%)** p=0.5	00 **(00)** p=0.6
Gastritis	00 **(00)** p=0.5	07 **(100%)** p=0.09	00 **(00)** p=0.2	00 **(00)**p=0.5
Peritonitis	00 **(00)** p=0.2	18 **(85.7%)** p=0.1	03 **(14.3%)** p=0.5	00 **(00)** p=0.2

DISCUSSIONS:

A total of 297 cases of Crohn's disease were identified during the period of 2007-2019. The median age for developing Crohn's disease was about 39 years. In same way, studies of [7] showed that the median age at diagnosis of CD patients was approximately 30 years. However, in the study of [8] the patients were younger, since the minimum age of onset of the disease was 12 years.

The majority of patients were more likely males which is consistent with the results of [9–11] but not with those of [7,12].

In our study, different segments of the digestive tract were affected, but colonic and ileo-cecal localizations were the majority. These results are similar to those reported in different studies by (**Adler et al, 2017; Can et al, 2015; Duarte-Silva et al, 2019; Herzog et al, 2018**).

All age groups showed colonic and ileocecal localization, which is consistent with the results of (**Herzog et al, 2018**). Whereas, the jejunal localization in our study was more present in the age groups of 20-80 years. However, it was noted in the patients under the age of 40 in the **Herzog** study.

Our results showed that the inflammatory and stenosing phenotypes were the most frequent, followed by complicated cases of fistulas and ano-perineal lesions as confirmed by the results of several authors (**Feuerstein and Cheifetz, 2017; Kugathasan et al, 2017**).
The inflammatory and stenosing types affected all age groups of our population, which is consistent with the results of (**Herzog et al, 2018**).

Moreover, we noticed that the most common symptoms in our patients were occlusive Sd, sub-occlusive Sd, abscess and fistula, which agrees with[13] findings.

The most altered biological signs in our patients were:

- CRP >11mg/L, Vs 1h (>7mm); 2h (>11mm) with non-significant association as reported by [14,15].
- Anemia in both men (<130) and women (<120) as noticed by [16,17].
- Only 2% of the patients carried out the serological assessment with an ASCA positive for the presence of the antibodies directed against the mannans in particular the Anti-Saccharomyces Cerevisiae "ASCA".

Gologan S et al (**2012**) have found that the highest IgA and IgG are linked to a younger age at diagnosis and to more aggressive phenotypes in Romanian patients with CD (**Huang et al,) (Gologan et al, 2012).**

7.1% of our patients had a positive TBC. Similarly, studies by (Rais et al., 2018) have noted that the digestive tract can also be affected by tuberculosis and considered to be a granulomatous disease. Therefore, it would be inappropriate and even dangerous to treat a patient who actually has Crohn's disease with anti-tuberculosis therapy.

Cytomegalo viruses were noted in 1.7% of patients, ECB in 6.8% of patients and Varicella zoster virus in 0.7% of patients as noted by (**Bengi et al, 2018). C**olonoscopy was the most frequent test of diagnostic with a rate of 79%, which is consistent with the results of [18]

Among the 295 studied cases; a highly significant association was found between inflammatory pathology and Crohn's disease (44.7%). Of these, 7.1% are peritonitis, 2.4% are gastritis, 1.7% are UC, 0.7% are villous atrophy and COPD. These results are similar to those of [19,20]. We also found 0.3% cases of meningitis and 01% of appendicitis in the under 20 age group with a significant rate. These results have been

proven by [6,21]. Other IPs were found in our study, namely ulcers that appear in the under-20 age group and inflammatory anemia that occurs at <20-40 years of age. Both with a significant association. This is consistent with the results of [7].

In order to control inflammation and to relieve pain in Crohn's disease, the first-line treatment prescribed is medication. The choice of drug and route of administration depends on the intensity of the symptoms and their location in the digestive system. In our study 24.1% of patients were treated with 5-ASA. This prescription was also noted in the study of (**Liu et al., 2016**). Only 13.6% of patients were treated with immunosuppressants to calm the inflammatory reactions. These drugs are generally used to maintain remission after attack therapy (**Hiller et al., 2019; Liu et al., 2016**). As surgical treatment 29.2% of patients underwent ileocaecal resection with ileocolic anastomosis, 13.9% underwent a right hemi-colectomy which is in accordance with the results of [8,22].

Joint damage is the most common extra-digestive manifestation in Crohn's disease. In our study, Arthralgia was the most common inflammatory extra-intestinal manifestations with a rate of 12.5%. It reaches significantly higher rates in the 20-60 age group. These results are identical to those of (Herzog et al, 2018). Other studies (Bae et al, 2017; Herzog et al, 2018; Hiller et al, 2019; Hsu et al, 2017) have shown that Crohn's disease develops signs of ankylosing spondylitis (AS) affecting joint including that of the spine. 7.5% of our patients have developed AS. However, in other studies (Bae et al, 2017; Bandyopadhyay et al, 2015; Subramaniam et al, 2015), arthritis was the most reported whereas in our study we noted only 2.4% of patients developing arthritis

Crohn's disease remains an unknown and as yet ill-defined disease, however, medical progress has made it possible to move towards the existence of other risk factors. In our study 22.4% of patients were smokers (also noticed by **Bandyopadhyay et al, 2015**); 6.1% of men were alcoholic and 17.3% of patients had an appendictomy. Ameta-analysis of several studies has shown that, despite the heterogeneity, there is still a higher relative risk of developing crohn's disease after appendectomy [6,23].

CONCLUSION:

This study has shown that the association of inflammatory pathologies and Crohn's disease is more common in males; it often affects young ages with an ileocecal location and dominated by extra-intestinal manifestations of lesions such as arthralgia.

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