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CHRONIC INFLAMMATORY BOWEL DISEASES IN PATIENTS WITH ORTHOPEDIC MANIFESTATION. COMPARISON WITH THE DATA REPORTED IN INTERNATIONAL LITERATURE

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SUMMARY

In inflammatory bowel disease (IBD) the suspected etiological cause is a dysregulation of the intestinal immune system, in which it is possible to determine a cross-like immune reactivity against the resident microbiota; this mechanism explains the existence of Lesniowski-Crohn's disease, a variant of IBD in which patients manifest osteoarticular problems that may also be the primary manifestation of the disease. The aim of this study was to compare some cases encountered by our research group at the University of Palermo with others reported in international literature on osteoarticular manifestations in IBD.

Introduction

The initial hypotheses concerning the cause of inflammatory bowel disease (IBD), centered on an infective mechanism, have since been proven wrong by thorough scientific studies. Today, newer theories include a multifactorial etiopathogenesis, involving hereditary genetic factors, intestinal flora and exogenous factors such as tobacco smoke and nutritional habits typical of the north American or western European societies, where the incidence of Crohn's disease (CD) is increasing. Among hereditary factors, it seems that in some subjects, the intestinal immune system recognizes as pathogenic bacteria the resident microbiota, activating an inflammatory cascade that subsequently self-fuels a production of pro-inflammatory cytokines [1]. In ulcerative colitis (UC), the lesions are commonly located in the rectum and extend to the entire colon in absence of alternate areas of undamaged mucosa. In UC, the mucosa appears hyperemic, and in severe cases, bloody and ulcerated with pseudopolyps. CD can involve any part of the intestinal mucosa, with a typically segmental lesion distribution, and presents unaffected areas of mucosa along the intestine. CD rarely affects the rectum, with a possible presence of fistulas, abscesses and/or anal stenosis [2]. Peripheral arthritis is common in Crohn's disease and worsens with exacerbations of the intestinal manifestations, often involving upper and lower large joints in an asymmetric, migratory and polyarticular manner [3,4].

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Ankylosing spondylitis (AS) is more frequent in CD than in UC, and its pathogenic activity does not coincide with the remission of intestinal symptoms obtained with the use of corticosteroids and colectomy; many patients with IBD and AS result positive for the histocompatibility antigen class B-27 (HLA-B27), while in cases of AS where HLA-B27 is negative, the likelihood of the patient also being affected by inflammatory bowel disease is increased [5]. Sacroiliitis occurs in both CD and UC with the same frequency, presenting symmetrically, and does not correlate with the intestinal symptoms.

Material and Methods

The data collected for the present article have been obtained from studies conducted at the University of Palermo between 2004 and 2011 by simple random sampling. In the classification of patient status, the medical history was considered. Some patients had already been studied for inflammatory bowel disease (IBD), and in these cases, our attention was directed towards understanding whether the arthritic symptoms were primary manifestations, or a complication of IBD. For other patients, a multidisciplinary clinical study was necessary, since the osteoarticular symptomatology was the first manifestation to be reported by the patient. The patients were assessed according to the following criteria: anamnestic - clinical, with functional test of the joints involved [1]; biochemical markers of inflammation, such as erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor; radiological assessment with x-rays, such as the Bennet and Burch classification for sacroiliitis [6]; endoscopy with biopsy and histological examination. Endoscopic examinations were performed at the outpatient endoscopy clinic of the U.O.C. of General Surgery and Transplantation of the Polyclinic of Palermo. The patients with rectal ulcerative colitis (UC) and arthritis were then analyzed (Table1); we begun with the hypothesis test for independence using the following formula:

$$\begin{cases} Ho = x^2 = 0 \\ H1 = x^2 > 0 \end{cases}$$

with a significance level = 0.05.

At this point, theoretical frequencies of independence were constructed: a= 82*78/128 = 49.96. From these, the other frequencies were derived (Table 2); the

	Patients with Arthritis	Patients without Arthritis	Total
Ulcerative Colitis	68	14	82
No Ulcerative Colitis	10	36	46
Total	78	50	128

Table 1: Contingency table, indicating patients with/without rectal ulcerative colitis and with/without arthritis, and relationships among the variables allowing the application of the Chi-Square model.

	Patients with Arthritis	Patients without Arthritis	Total
Ulcerative Colitis	49,96	32,04	82
No Ulcerative Colitis	28,04	17,96	46
Total	78	50	128

Table 2: Contingency table, indicating the expected data (control value) of patients with rectal ulcerative colitis and arthritis.

	Crohn's disease	Without Crohn's disease	Total
Arthritis	45	33	78
No Arthritis	15	35	50
Total	60	68	128

Table 3: Contingency table, indicating patients with/without arthritis in the rows, and patients with/without Crohn's disease in the columns, and the relationships between them, enabling the application of the Chi-Square model.

empirical frequency analysis resulted different from the theoretical, indicating a relationship between the variables examined. By calculating the chi-square x^2: $x^2 = (|68-49.96| - 0.5)^2 / 49.96 + (|14-32.04| - 0.5)^2 / 32.04 + (|10 - 28.04| - 0.5)^2 / 28.04 + (|36-17.96| - 0.5)^2 / 17.96 = 46.275$. The critical chi-square, derived from the statistical tables, had a degree of freedom equal to 1 and a significance level of $\alpha = 0.05$, is 3.84. The area of waste was therefore $x^2 \geq 3.84$. By comparing the empirical chi-square with the critical one (46.275>3.84), the hypothesis of independence can clearly be rejected, and an obvious dependence between the two variables can be observed. The empirical p-value and Cramer's V value obtained further confirm these data by highlighting the strength of this association: p-value was found to be <0.001, while Cramer's V was =0.60. Different methods were used to further validate these findings, including the odds ratio and confidence interval (Table 1).

The application of the odds ratio formula produced the following result: OR=ad/bc (68*36)/14*10=17.48. This shows that the group of patients with UC is 17.48 times more likely to have arthritis than those who are not affected by UC. Next, the confidence interval for OR level of 95% was calculated: ln $\widehat{OR}$ ± 1.96 *Es ln $\widehat{OR}$.

ln 17.48 ± 1.96* $\sqrt{1/68 + 1/14 + 1/10 + 1/36}$ =

ln17.48 ± 1.96*0.4625= 2.86 ± 0.9065

2.86 – 0.9065 = 1.9546; ln 1.9546= 7.06.

2.86 + 0.9065 =3.7665; ln 3.7665= 43.23.

These data show that, at 95%, when the OR of the population falls between 7.06 and 43.23, there is a significant association between ulcerative colitis of the rectum and arthritis.

Our second research goal was to investigate whether a significant association between arthritis and Crohn's disease (CD) exists (Table 3).

In order to verify this hypothesis, a test for independence was performed:

$$\begin{cases} Ho = x^2 = 0 \\ H1 = x^2 > 0 \end{cases}$$

The significance level was equal to α=0.05. At this point, the theoretical frequencies of independence were constructed: a=78*60/128=36.56. All other parameters were derived from this data (Table 4).

A difference in the theoretical and empirical frequencies was observed, confirming an association between the variables examined. By calculating the chi-square x^2, the degree of freedom and significance level

	Crohn's disease	Without Crohn's disease	Total
Arthritis	36,56	41,44	78
No Arthritis	23,44	26,56	50
Total	60	68	128

Table 4: Contingency table, indicating the expected values (control) of patients with Crohn's disease and arthritis.

were fixed at $\alpha = 0.05$. Given the degree of freedom, a correction had to be applied to the model: $x^2 = (|45-36.56|-0.5)^2/36.56+(|33-41.44|-0.5)^2/41.44+(|15-23.44|-0.5)^2/23.44+(|35-26.56|-0.5)^2/26.56 = 9.436$. The critical chi-square was derived from the statistical tables: with a degree of freedom equal to 1 and a significance level $\alpha=0.05$, the result was 3.84. The area of waste was therefore $x^2 \geq 3.84$. By comparing the empirical chi-square with the critical one (9.436>3.84), the hypothesis of independence can clearly be rejected, and a relationship between the two variables can be postulated. The p-value and Cramer's V value of 0.001<p-value<0.001 and V=0.27, further confirms this finding. Using the Cramer's V value, we found that the strength of the relationship between the two variables is modest. For further confirmation, different methods, including the odds ratio and its confidence interval (Tab. 3) were applied: OR=ad/bc (45*35)/33*15=3.18. This means that patients with arthritis are 3.18 times more likely to also have Crohn's disease, compared to those without arthritis. Taking into account the confidence interval of 95%, the following result was obtained:

$$\text{Ln}\ \widehat{OR} \pm 1.96 * \text{ESln}\ \widehat{OR} = \text{Ln}\ \widehat{OR} \pm 1.96 * \sqrt{1/45 + 1/33 + 1/15 + 1/35} =$$

Ln 3.18 ± 1.96 * 0.3844 = 1.15 ± 0.7534,

1.15-0.7534= 0.3966 ln 0.3966= 1.49

1.15+0.7534= 1.9034 ln 1.9034= 6.71

This indicates that the odds ratio for the population falls between 1.49 and 6.71, confirming the findings described above.

Results

Altogether, 128 patients were studied. 82 (64.06%) of these suffered from ulcerative colitis (UC) (mean age 55,5 years, range 19 -75 years), and 60 from Crohn's disease (CD), with only 45 (35.16%) (mean age 54,1 years, range 17-75 years) having a firm diagnosis, while the remaining 15 patients presented an unclear clinical picture and were therefore under further investigation. A breakdown of joint involvement presents the following topography: arthritis of the hip was present in 12 patients (50%), while arthritis of the shoulder was present in nine patients (37.5%); 22 patients (91.6%) had peripheral arthritic involvement (in detail, 10 patients presented knee involvement, and eight patients ankle involvement); among the patients with osteoarticular complications of inflammatory bowel disease, six (25%) were affected by spondylitis, and four (16.67%) by sacroiliitis. Our results are compared with the findings from international literature in Figure 1 and Figure 2.

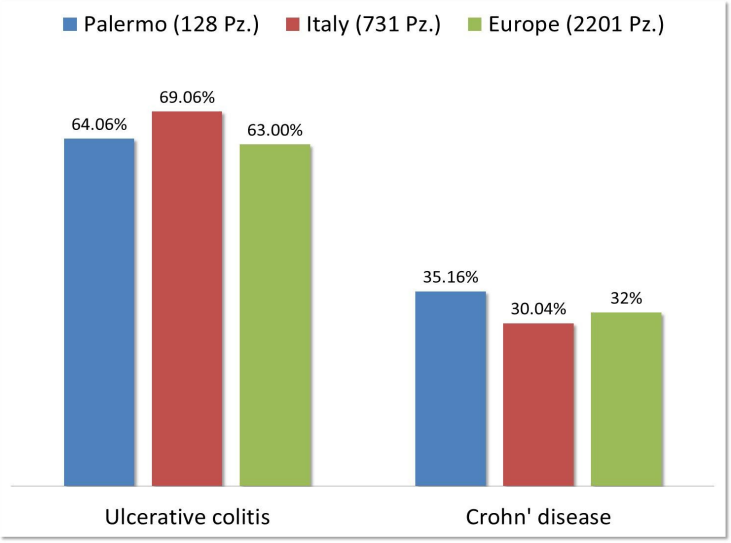
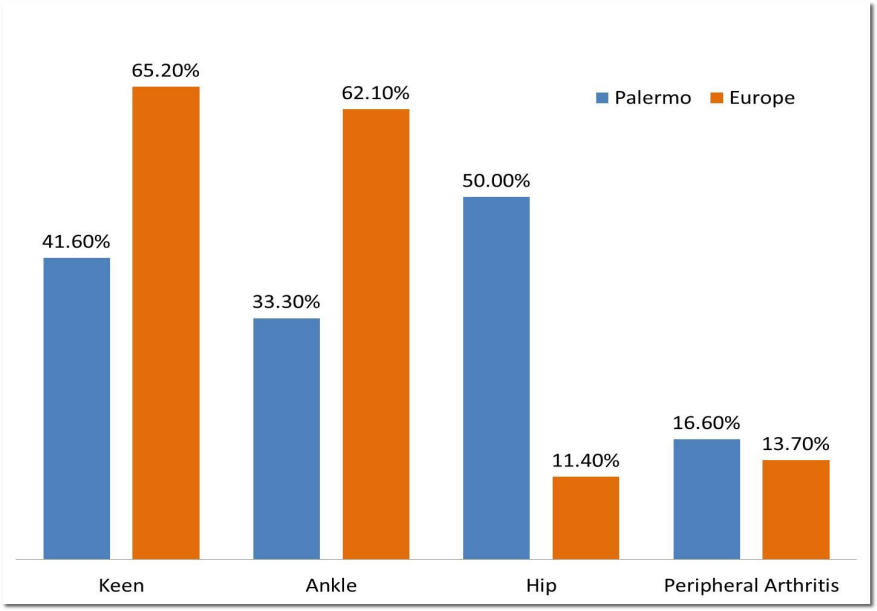


Figure 1: Related prevalence data of Inflammatory Bowel Diseases in Palermo, Italy and Europe. The trend observed during our study is nearly identical to that of the European context.

Figure 2: Anatomical distribution of joint involvement during the course of inflammatory bowel disease. The prevailing European trend sees the involvement of the knee and ankle, while our study in Palermo found a greater affection of the hip. In both cases, the lower limbs are the most involved.



Discussion

In the present study, our aim was to analyze existing data concerning statistical trends of inflammatory bowel disease (IBD), as well as those of arthropathies occurring during the course of IBD. The prevalence of IBD, including 64.6% of patients with ulcerative colitis and 35.9% with Crohn's disease, found during our study, is completely superimposed compared with previous Italian data by Tragnone et al. [7], but similar to the prevalence rates found in Europe according to a study by Shivananda et al. [8] Slight differences, however, are found in the data on the prevalence of arthropathies in IBD. We found moderate increase in the prevalence of osteoarticular manifestations of IBD, compared to the results of Palm and colleagues [9]. This difference could be explained by the findings of other studies analyzing the incidence of IBD (see Shivananda et al.), from which it is clear to see that the incidence of ulcerative colitis, and, especially, Crohn's disease, is increasing together with IBD-related arthropathies. The clinical features observed in our series are asymmetric symptoms, joint involvement of a migrant nature, which is often polyarticular. From our analysis, it can be noted that the anatomical sites involved in the arthritic process include mainly the large joints of the lower limbs, with the only difference with the previous study by Yukel et al. being the primary involvement hip in our study, whilst in the former, the knee and ankle resulted to be most affected. Our study also aimed to determine whether there is a significant relationship between rectal ulcerative colitis and arthritis, and/or Crohn's disease and arthritis. To this end, a simple random sample of 128 patients, including 82 with rectal ulcerative colitis, was selected. In this group, 68 patients were also affected by arthritis (tab. 1). With the initial chi-square statistic test, we found a value that amounted to 46.275, resulting significant for $\alpha = 0.05$ ($46.275 > 3.84$) and a p-value of < 0.001; these results prove that there is a significant relationship between rectal ulcerative colitis and arthritis. Although the chi-square test allowed us to determine the association between the two variables, it does not provide means to measure the strength of this association. Therefore, we proceeded by calculating the Cramer's V value, normalized within the range of 0.1; with a result of 0.60, this shows the presence of a fair degree of dependence.

Finally, the odds ratio was calculated: the sample data resulted to have a value of 17.48, showing that the risk of also having arthritis in the group of patients with UC is 17.48 times higher compared to the non-affected group. It also provides the confidence interval limits for the population; at 95% of the population, the odds ratio was between 7.06 and 43.23. To test our second research hypothesis, and determine whether there is a significant relationship between arthritis and Crohn's disease, we proceeded similarly: of the 78 patients with arthritis, as many as 45 also had Crohn's disease (Tab. 2); the statistic test resulted in a value of 9.436 which is significant for $\alpha = 0.05$, and it could therefore be concluded that there is a significant association between the two variables. To quantify the strength of the relationship between these variables (arthritis and Crohn's disease), we calculated Cramer's V value, which was equal to 0.27, showing a modest association. Following the calculation of the p-value, which was between 0.01 and 0.001, an odds ratio of 3.18 was determined. These data show that the risk of Crohn's disease is 3.18 times higher in patients with arthritis than in the non-affected group. Again, we calculated the 95% confidence interval of odds ratio of the population, found to be between 1.49 and 6.71. In synthesis, with reference to the first research hypothesis, it can be concluded that patients with rectal ulcerative colitis are more likely to have arthritis than those who do not have this type of ulcerative colitis. With reference to the second hypothesis, it can be concluded that patients with arthritis have a greater chance of developing Crohn's disease compared to patients without arthritis. The three main results that emerge from our analyses are:

- the incidence of chronic inflammatory bowel disease is increasing, together with the related articular manifestations.
- the prevalence of IBD is stable in the European context.
- the joint most affected in our area (Palermo) is the hip, while in the European context, knee and ankle are the most affected joints.

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