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HEAT SHOCK PROTEINS AND AUTOIMMUNE SYSTEM ACTIVATION IN IBD: ARTICULAR MANIFESTATIONS AND THEIR EPIDEMIOLOGICAL FREQUENCY IN ORTHOPEDICS

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[Attivazione del sistema immune e proteine da shock termico nelle malattie infiammatorie croniche intestinali: manifestazioni articolari e loro frequenze epidemiologica nei controlli ortopedici]

ABSTRACT

Clinical evidence suggests that arthritis is one of the complications of inflammatory bowel disease (IBD) of which the etiological causes are still not completely understood. Among the possible explanations the most probable theory is poor regulation of the intestinal immune system, which causes a cross-like immune reactivity against the resident micro flora. Arthritis in these subjects involves different joints and is asymmetric, with greater involvement of the large joints of the lower limbs. Joints may also be involved with the spinal forms of sacroileitis and ankylosing spondylitis. This clinical evidence explains the existence of Lesniowski-Crohn's disease, a variant of IBD in which patients have bone joint problems that may also be the primary manifestation of the disease.

Key words: IBD, HSP, arthritis, microbiota.

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Introduction

Chronic inflammatory bowel disease (IBD) is increasing in industrialized countries, and this suggests a role for exogenous factors, such as tobacco and a high calorie diet, in the etiology of these diseases[1,2,3]. Several studies draw attention to the abnormalities, due to exogenous insults, of the saprophytic commensal micro flora with subsequent damage to tight mucosal joints with loss of impermeability. This causes penetration of bacterial antigens into the intercellular space with activation of the mucosa-associated immune system. Correlated with the loss of impermeability of the mucosa, other studies have shown that the migration of macrophages and intestinal lymphocytes is responsible for the onset of joint inflammation; this has been evidenced due to the finding, in synovial fluid, of antigens and bacterial genetic material, often of gram-negative bacteria able to invade and survive within the host cell, by use of polymerase chain reaction[4]. All this can be compatible with the intestinal origin of these bacteria. Genetic alterations of the histocompatibility complex B-27 (HLA-B27) and polymorphism of the receptor for interleukin 23 (IL-23R) increase the risk and susceptibility of developing IBD when exposure to exogenous environmental factors exist[5]. 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 pseudo-polyps. Crohn's disease (CD) can involve any part of the

intestinal mucosa, with a typically segmental distribution of the lesion, and there are unaffected areas of mucosa along the gut. CD rarely affects the rectum, with a possible presence of fistulas, abscesses and/or anal stenosis. Peripheral arthritis is common in CD and worsens with exacerbations of the intestinal manifestations, often involving multiple upper and lower large joints in asymmetric, migratory ways[6].

The histological-pathological framework in arthritis secondary to chronic inflammatory bowel disease appears similar to that of rheumatoid arthritis due to the presence of synovial hypertrophy, lymphoid infiltrate and synovial pannus development. The characteristics that identify arthritis as a complication of inflammatory bowel diseases are the presence of cartilage erosions at the center of the joint surface, quite different from erosion type, tail of mouse and lesion without fish scale present only on synovial areas, distinctive of rheumatoid arthritis. For this reason the best approach for the physician is a multi-disciplinary one, in both diagnostics and therapy.

Materials and methods

Collected data were 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. In acute involvement joints appear swollen, due to the presence of effusion, redness, and with loss of normal joint profile; pain was present both at rest and during passive movement; altered range of motion with a moderate degree of functional impairment may also be found. In some patients induction of loco-regional analgesia was necessary in order to perform the specific semiological test of involved joints.

The diagnostic procedure is continued with the evaluation of inflammation bio-humoral values such as the leukocyte formula, erythrocyte sedimentation rate, C-reactive protein (CRP), and rheumatoid factor. X-ray investigations were performed to properly stage the degeneration of cartilage in the involved joints. Endoscopic examinations with biopsy and histological examination were performed at the outpatient endoscopy clinic of the Department of Surgery, Faculty of Medicine, University of Palermo.

Results

Altogether, 128 patients were studied: 82 (64.06%) suffered from ulcerative colitis (UC) (mean age 55.5 years, range 19-75 years), and 60 from CD, with only 45 (35.16%) (mean age 54.1 years, range 17-75 years) having a firm diagnosis, while the remaining 15 patients had an unclear clinical picture and therefore underwent further investigation. One patient with CD was excluded for poor compliance (Table 1). A breakdown of joint involvement exhibits 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 (10 patients had knee involvement, and 8 patients ankle involvement); among the patients with bone joint complications of inflammatory bowel disease, six (25%) were affected by spondylitis, and four (16.67%) by sacroiliitis[7].

OVERVIEW TOTAL PATIENTS	
ENROLLED	143
WITH ULCERATIVE COLITIS	82
WITH CROHN'S DISEASE	46*
EXCLUDED FOR UNCERTAIN DIAGNOSIS	15
*EXCLUDED FOR POOR COMPLIANCE	1

Table 1: Patients enrolled and their distribution by diagnosis.

Our study also aimed to determine whether there is a significant relationship between rectal ulcerative colitis and arthritis, and/or CD 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 also had arthritis. With the initial chi-square statistic test, we found a value that amounted to 46.275, which was 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 any 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 had 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 unaffected group. It also provides the confidence interval limits (95%) for 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 CD, we proceeded similarly: of the 78 patients with arthritis, 45 also had CD; the statistical test had 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 CD), 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 found. These data show that the risk of CD is 3.18 times higher in patients with arthritis than in the unaffected group. Again, we calculated the odds ratio of the population (95% confidence interval), which was 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 CD compared to patients without arthritis.

Our results are compared to the findings from the international literature in Figure 1 and Figure 2.

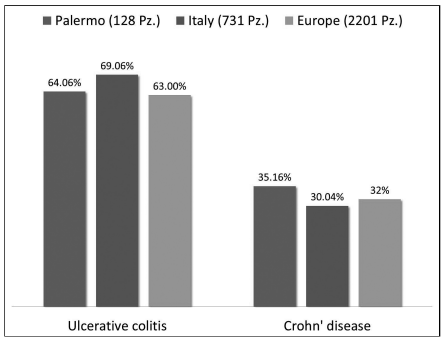

Fig. 1: Relative prevalence data of inflammatory bowel disease in Palermo, Italy and Europe. The trend observed during our study is nearly identical to that of the European context.

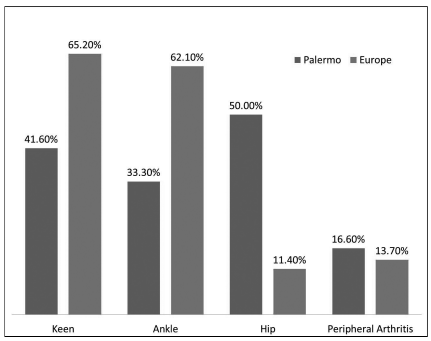

Fig. 2: Anatomical distribution of joint involvement during the course of inflammatory bowel disease. The prevailing European trend is the involvement of the knee and ankle, while our study in Palermo found a greater prevalence of the hip. In both cases, the lower limbs are the most involved.

Discussion

The prevalence of IBD, including 64.6% of patients with ulcerative colitis and 35.9% with CD, found during our study, is completely consistent with previous Italian data by Tragnone et al.[8], but similar to the prevalence rates found in Europe according to a study by Shivananda et al.[9]. 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; the only difference is with the previous study by Yukel et al.: in our study the primary involvement of hip, whilst in the former, the knee and ankle were most affected.

The management of patients with IBD arthritis is very complex due to the need for multidisciplinary clinical intervention that should be performed to respond to requirements of the patients established during the medical examination. From the moment the patient has received the communication of a definitive diagnosis of inflammatory and chronic disease there is a period of considerable psychological stress. In orthopedic units the main request of the patients was the need to be able to live without pain and with improved joint function.

Satisfactory results were obtained with the use of intra-articular viscosupplementation therapy with high molecular weight hyaluronic acid sodium salt: 1.5% at dosages of 30 mg (for the major joints), administered every week for 3-4 weeks[10]. In synergy with infiltrative therapy, repeated physiotherapy has improved the elasticity of capsular and pericapsular soft tissue increasing joint range of movement (ROM). In cases in which the cartilage degeneration was severe, with initial signs of ankylosis, prosthetic surgery was recommended to the patient. In our opinion anti-inflammatory therapies with fans are absolutely contraindicated, due to their

injurious effect on gastric mucosa, already eroded by the pathogenic mechanism of IBD[11,12]. Most patients with IBD had therapy with 5-amino salicylic acid (5-ASA) in combination with probiotics. The 5-ASA performs an anti-inflammatory action that is expressed at the level of the epithelial cells of the colon. The drug is administered as a pro-drug which requires the action of specific enzymes produced by the commensal microflora to be activated.

This is a reason for therapeutic association of 5-ASA with probiotics, which, by increasing the concentration, at the level of the mucosa, of the azoreductase enzyme, promotes the increase in concentration of 5-ASA activated; thus resulting in a better therapeutic response: levels of complications from overdose declined significantly. Clinical trials at the University of Palermo evaluated the response to treatment with 5-ASA plus probiotics[13], measuring the levels of heat shock proteins (HSP) in frustules of mucosa taken from the colon. Then results were compared with the levels of HSP found in frustules of mucosa of patients who received only 5-ASA. The studies were conducted at the Institute of Normal Human Anatomy of the Polyclinic Hospital, Palermo; the HSPs evaluated were the HSP 60, HSP 10, HSP 70, HSP 90. Laboratory data showed that in patients who performed the combined therapy (5-ASA plus probiotic) levels of HSP 60, HSP 10 were reduced significantly both at epithelial and at the sub-epithelial level after six months of treatment. HSP 70 is significantly reduced only in the epithelial layer and HSP 90 was reduced exclusively only at the sub-epithelium layer and only in patients receiving 5-ASA plus probiotics[14,15,16]. The main results that emerge from our analyses are:

• 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.

• biological therapies with probiotics and ac. hyaluronic acid are essential adjuvants for medical treatment of the patient with IBD.

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