

## Ankylosing Spondylitis or Crohn's Disease? Case report and review of the literature

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A 27-year-old male with a 2 year history of ankylosing spondylitis (AS) was investigated for intermittent episodes of diarrhea and found to have granulomatous ileitis. Differential diagnosis, discussions regarding similarities in immune alterations in both AS and Crohn's disease and therapeutic options are presented in this paper.

**Key words:** ankylosing spondylitis, Crohn's disease, granulomatous ileitis.

### CASE REPORT

R.M.G., a 27-year-old Caucasian man with a 2 year history of ankylosing spondylitis (AS) was referred to the Gastroenterology Department for the investigation of intermittent diarrhea during the last 5 years consisting in episodes of 4–7 unformed stools/day for 2–3 weeks, 2 or 3 times/year. There was no relevant family history. His rheumatologic diagnosis relied on the lumbar and thoracic vertebral inflammatory pain, the reduction of the spine mobility and radiographic changes of bilaterally grade II sacroiliitis, without HLA-B27 antigen. Three years ago, he underwent a colonoscopic examination, which revealed only a small area of erythematous mucosa in the sigmoid colon, histologically described as non-specific inflammation of the mucosal layer; the terminal ileum was then not evaluated. He was administered sulfasalazine, but the treatment was discontinued 1 week afterwards due to abdominal discomfort, a possible side effect of the drug being considered. The patient denied taking any medication for the AS symptoms in the last year.

Physical examination revealed the lumbar inflammatory pain and the reduction of the spine mobility. The BASDAI score was 2.8. All the blood tests results (including inflammation markers – erythrocyte sedimentation rate, fibrinogenemia and serum C reactive protein) were in the normal range. Further investigation detected a high fecal calprotectin level (qualitative assay 3+) suggestive for intestinal inflammation.

The patient was further investigated for inflammatory lesions of the small bowel and/or of the colon using capsule endoscopy and colonoscopy, respectively. At capsule endoscopy, in both jejunum and ileum several small aphthous ulcers were identified and in the terminal ileum there was an area of mucosal edema and erythema, comprising also several petechiae and small aphthous ulcerations (Fig. 1). This area was accessible during ileocolonoscopy and tissue biopsies were taken. No colonic macroscopic lesions were found.

Histological evaluation of the ileal biopsies revealed mixed acute and chronic inflammatory cells that involved mucosa, muscularis mucosae and submucosa, with a fissure extending from the base of an aphthous ulcer to the submucosa, and a granuloma in the submucosal layer (Fig. 2).

The patient was given 2 grams of mesalazine orally per day, with remission of the diarrhea, but evaluation 6 months later revealed the same high fecal calprotectin level (qualitative assay 3+) suggestive for persistence of the intestinal inflammation, despite no intestinal symptoms; mild low-back inflammatory pain still persisted, and the BASDAI score was 2.5.

### DIFFERENTIAL DIAGNOSIS

On the basis of the clinical history, signs and symptoms and laboratory findings there is little doubt about the diagnosis of ankylosing spondylitis in this case (modified New York criteria fulfilled),

with the BASDAI score proving there is a mild form of the disease. Given the presence of an associated granulomatous ileitis which has many potential causes, however, there is a wide differential diagnosis.

### **Intestinal infection**

Infection with *Y. enterocolitica* and *Y. pseudotuberculosis* could be associated with granulomatous ileitis and reactive arthritis with some of the features of a spondyloarthropathy, mostly in HLA-B27 positive individuals [1]. In this case, however, the patient had not been to an area endemic for *Yersinia* spp., is HLA-B27 negative, the clinical picture is not dominated by fever or abdominal pain, and the aphthous ulcers involve the entire small bowel, not only the ileum. For these reasons, infection with *Yersinia* spp. is unlikely to explain this patient's presentation.

Reactive arthritis may occur also after an enteric infection due to *Salmonella*, *Shigella*, or *Campylobacter* species, but is not associated with intestinal granuloma formation.

The gastrointestinal tract can represent the site of infection with both *Mycobacterium tuberculosis* and *M. bovis*. Intestinal tuberculosis usually causes large ileocecal ulcers (not present in this case), and the pathological features include caseating granulomas [2]. The most important findings that argue against a diagnosis of intestinal tuberculosis in this patient were absence of acid-fast bacteria on histology and the presence of small, noncaseating granulomas.

Measles can also cause a granulomatous ileitis, but this ileitis occurs in the setting of disseminated disease [2].

### **Intestinal Sarcoidosis**

Intestinal sarcoidosis is very rare and patients usually present with respiratory, skin and also eye symptoms [3]. Lymphatic obstruction, which this patient did not have, is a characteristic intestinal finding of this condition [3]. Absence of other manifestations of the disease makes this diagnosis very unlikely. Testing for the serum level of angiotensin-converting enzyme is probably not indicated in this case, but if performed, its normal level rules out the disease.

### **NSAID enteropathy**

Most patients with ankylosing spondylitis are treated with non-steroidal anti-inflammatory drugs (NSAIDs), which are a potential cause of ulcerations and/or inflammatory changes of the small-bowel

(NSAID enteropathy). The typical patient is one taking NSAIDs for a rheumatic condition, the duration of NSAID use to time of diagnosis is widely variable (days to years), and it seems that there is no difference in development of bowel lesions between those taking COX-2 selective or non-selective NSAIDs [4]. This condition is usually asymptomatic. We must emphasize that the patient denied taking anti-inflammatory medication for his lumbar pain.

Localization of the most important inflammatory lesion to the terminal ileum (rather than mid small bowel) would be unusual even if the patient had taken over-the-counter NSAIDs. Also worth mentioning, there have been no reports of granulomatous reactions in intestinal biopsies from patients with NSAID enteropathy [5].

### **Ileitis of spondyloarthropathy or Crohn's disease?**

Ileocolonoscopy reveals subclinical intestinal inflammation in approximately 60% of patients with ankylosing spondylitis, predominantly in the terminal ileum [6]. The gut lesions found in patients with ileitis associated with AS are divided histologically into acute (neutrophil dominant) or chronic (lymphocyte dominant). The chronic type, which is the most frequently encountered, closely resembles ileal Crohn's disease (CD), as the mucosal architecture is clearly disturbed, the villi are irregular, blunted and fused; the crypts are distorted and the lamina propria is edematous and infiltrated by mononuclear cells. In some cases aphthous ulcers and sarcoid-like granulomas are present [7]. Worth mentioning, the presence of chronic ileal lesions might be a predictor of an aggressive evolution of the spondyloarthropathy (SpA)[7].

Fecal calprotectin is the only biological marker of intestinal inflammation that is present in this patient. Calprotectin is a major protein found in the cytosol of inflammatory cells [8]. A considerable proportion of patients with a false positive test result will, however, prove to have a gastrointestinal condition different from IBD, such as intestinal infection, intestinal lymphoma, NSAID-induced bowel lesions, and autoimmune enteropathy, among others [8]. It is considered that increased fecal calprotectin levels may indicate a need for endoscopy, whereas normal calprotectin levels are less likely to be associated with intestinal inflammation and further investigations could be tailored appropriately [8].

Suspicion of Crohn's disease (CD) is raised in SA patients with diarrhea that is persistent ( $\geq 4$  weeks) or recurrent ( $\geq 2$  episodes in six months). Patho-

gnomonic signs or symptoms do not exist. Endoscopic evaluation with histopathologic sampling is generally considered indispensable in the investigation of patients with suspected Crohn's disease (such as this case, with clinical context of associated AS, suggestive symptoms and positive markers of intestinal inflammation). Ileoscopy should always be attempted in patients with suspected Crohn's disease, because it adds little or no risk to a diagnostic colonoscopy and can be routinely accomplished by an experienced endoscopist in most patients [9] [10], and biopsies of the terminal ileum should be taken [11].

Predominant involvement of the terminal ileum, as in this case, is highly suggestive of Crohn's disease. The spondyloarthropathy associated with Crohn's disease can only be distinguished from idiopathic ankylosing spondylitis by the prevalence of HLA-B27, which, while still high, is significantly lower in patients with Crohn's disease than in those with ankylosing spondylitis. Classic IBD, however, precedes the development of spondylitis in most cases. On the other hand, a small proportion (<5%) of patients with established spondyloarthropathy can develop classic IBD within 10 years of the primary diagnosis: 80% of patients develop Crohn's disease and 20% ulcerative colitis [12].

Curiously, the main risk factor for IBD in patients with established ankylosing spondylitis is the absence of HLA-B27 (80% of cases), as is the case of the patient presented here [13].

Therefore, at this point we cannot classify the granulomatous ileitis present in this patient as ileitis of SpA or Crohn's disease. The only thing that we could say is that he is at high risk for developing the latter, if not already having it.

## DISCUSSION

From a researcher's point of view, the interaction between intestinal inflammation and arthropathy is a fascinating one. Studies show that half of all first-degree relatives of patients with either CD or AS have subclinical intestinal inflammation that is inherited according to an additive trait [14]. Both disorders have high heritability scores and patients with both diseases are significantly more closely related than controls. These findings suggest that ileitis and arthritis are causally related [14].

Some of the discovered similarities in the immune alterations in CD and SpA are: an increased expression of  $\alpha E/\beta 7$  in T-cells from patients with SpA and in the intestinal lymphocytes of patients with CD; an increased expression of epithelial A-cadherin; an increased expression of CD 163 positive macrophages in CD and SpA; relative contribution of T-helper 1 cells; and presence of IgA antibodies to *Saccharomyces cerevisiae* [14] [15].

Up to two-thirds of patients with AS have subclinical gut inflammations shown either by endoscopy or histology [7] [16]. A fraction of the AS patients go on to develop clinically overt CD [13]. It could be speculated that SpAs and CD probably should be considered as distinct phenotypes of a common immune-mediated inflammatory disease pathway rather than as separate disease entities and that ileitis of SpA might actually represent subclinical Crohn's disease [14].

Therefore, at present, ileitis associated with ankylosing spondylitis cannot easily be distinguished from Crohn's disease, either macroscopically or microscopically. In these patients, the experience of regular episodes of diarrhea early in the disease history, the persistence of raised inflammatory serum parameters, and the presence of chronic inflammatory gut lesions were found to be risk factors for the development of IBD. HLA-B27 negativity in the presence of sacroiliitis has been considered an important risk factor for inflammatory bowel disease (IBD) [13].

## THERAPEUTIC OPTIONS

The ileum is the most common region of the small bowel involved in Crohn's disease. Some authorities do not feel compelled to treat patients with Crohn's ileitis who are minimally symptomatic, because whether any treatment alters the natural history of the disease in such patients is unproven. Nevertheless, the granulomatous chronic ileal inflammation detected on the biopsy in this case predicts that this patient is prone to having an aggressive form of spondyloarthropathy, which might represent an indication for early aggressive intervention.

## NSAIDs

In AS patients there is a rapid remission of the symptoms with NSAIDs administration, but they do not stop the progression of the rheumatologic disease. 70 to 80 percent of AS patients

report substantial relief of their symptoms with NSAIDs [17]. Unless contraindicated because of comorbidity, NSAIDs should be the first line of treatment for all symptomatic AS patients [18].

Knowing the fact that the NSAIDs can lead to exacerbation of preexisting IBD [19], there are some concerns regarding administration of NSAIDs in cases like this. However, our work proves that the distal small bowel of spondyloarthritis patients is not affected by NSAIDs consumption [20].

Therefore, for controlling the articular symptoms, we consider that NSAIDs can be used with caution in this case.

### 5-ASA Drugs

Oral 5-ASA agents are largely used for the treatment of IBD, being effective both for the treatment of active CD, and especially for maintenance of remission [21]. They are not useful for the lesions involving other parts of the small bowel other than the distal ileum, because the drug needs to be splitted by the bacterial azoreductases from the gut in order to become active. The precise mechanisms responsible for the clinical efficacy of 5-ASA compounds are not known. However, *in vitro* investigations have identified many anti-inflammatory and immunosuppressive properties of 5-ASA, suggesting a multifactorial basis of its therapeutic action [22].

In CD patients with mild symptoms, as the case presented here, the treatment is usually begun with a slow release oral 5-ASA agent. However, with 4 grams per day, there is only an overall *modest* reduction in disease activity compared with placebo (the mean reduction in the Crohn's Disease Activity Index was reported to be 67 points, 25 points better than with placebo) [21]. In contrast to mesalazine, sulfasalazine is less useful for ileitis. The diminished response probably reflects the need for colonic bacteria to cleave the drug to release the active 5-ASA moiety [23].

There were small studies in SpA patients with terminal ileitis receiving 5-ASA drugs and the reduction of the bowel inflammation was confirmed [7]. However, with regard to the articular symptoms in AS, mesalazine or sulfasalazine are not effective for the axial involvement, present in the case discussed [18] [24].

Therefore, in this case, as mesalazine in doses of 2 grams per day were not effective in controlling the intestinal inflammation, an option would be to increase its dose up to 4 grams per day and reevaluate the patient after another few weeks.

### Antibiotics

For patients with Crohn's disease who do not respond to or do not tolerate 5-ASA drugs, it is a common practice to initiate a trial of one of several antibiotics as primary therapy before beginning glucocorticoids. It is unclear if the efficacy of antimicrobial therapy is due to treatment of an undetected pathogen or of bacterial overgrowth [25].

Whether this approach is useful in the subset of AS patients with ileal granulomatous inflammation, it remains to be proven.

### Corticosteroids

Chronic administration of systemic corticosteroids is generally not recommended in AS, because they are rarely effective and serve to promote decreased bone mineral density, although injection of a long-acting corticosteroid into painful sacroiliac joints may relieve pain in patients whose symptoms are refractory to NSAIDs. The efficacy of systemic glucocorticoids in AS has not been assessed in clinical trials [18] [26].

On the other hand, however, in CD, prednisone continues to be a mainstay of treatment for patients with mild disease who are unresponsive to the above mentioned measures [27]. Controlled ileal release (CIR) budesonide, a glucocorticoid with a high first-pass hepatic metabolism may be used as an alternative to prednisone in patients with mild to moderately active Crohn's ileitis, with potential fewer side effects. It is used at a dose of 9 mg/day for 8 to 16 weeks and then discontinued over two to four weeks by tapering in 3 mg increments.

We suggest using the above-mentioned measures to achieve remission of the ileal inflammation in this patient, if not obtained with 4 grams/day of mesalazine, and then maintenance therapy with a 5-ASA drug once control of active ileitis has been achieved, at a dose of 2–3 grams/day, should be considered as long-term therapy with the hope of preventing disease relapse [28]. However, it must be acknowledged that there is inconsistent evidence supporting this approach, and the articular symptoms will probably not be influenced.

### DMARDs

There is a paucity of data regarding the use of immunosuppressive and disease-modifying anti rheumatic drugs (DMARDs) in the diseases included in the concept of SpA. Despite this, they are commonly used in the different SpAs. On the other

hand, there is evidence that they favorably influence the bowel inflammation, when administered in different forms of IBD.

A common and challenging problem is the patient who remains symptomatic despite adequate doses of steroids (not used in this case). An evolving trend among some authorities in the field of IBD has been to use the immunomodulatory agents early in the course of disease before patients become steroid-dependent or resistant [25].

For refractory patients with Crohn's ileitis, the major alternatives are azathioprine or its active metabolite 6-mercaptopurine (6-MP). The response rate to these medications is 60 to 70 percent and will usually be seen within three to six months. Patients receiving these drugs require regular monitoring for toxicity [25]. Methotrexate is an alternative for the patient who does not tolerate or is unresponsive to azathioprine or 6-MP and may be used in preference to azathioprine or 6-MP in patients with troublesome Crohn's disease-related arthropathy, such as this patient. However, a 2006 meta-analysis of the efficacy of methotrexate for the articular symptoms in AS found no evidence of a beneficial effect in this disease [29]. Moreover, the use of the combination of methotrexate and infliximab did not increase efficacy or decrease the risk of adverse effects compared with infliximab alone [30].

### Biological agents

Part of the inflammation in both AS and Crohn's disease is believed to result from the generation of cytokines by antigen-stimulated T cells. Elevated concentrations of TNF mRNA are found in the inflamed gut of patients with Crohn's disease [31], and in the inflamed sacroiliac joints of patients with AS [18].

As the gut inflammation in Crohn's disease is mainly dependent upon Th1 cytokines [25], the joint inflammation seems to be more dependent upon Th2 cytokines [32] [33]. No in situ data are available on cytokine expression in the gut in SpAs. Biological compounds, such as cytokines, anti-cytokines as well as compounds interfering with recirculation have been applied in research protocols for selected groups of patients. Since some of these interventions interact specifically with gut inflammation, it is tempting to speculate upon their effect in patients with ileitis of SpA.

There are some differences seen with different biologic agents between CD and AS. Three anti-TNF therapies are approved for treatment of Crohn's disease in adults and all are effective in treatment of luminal Crohn's disease: infliximab,

adalimumab, and certolizumab pegol [34]. Clinical trials and experience have demonstrated their significant utility for induction of remission in moderately active, steroid refractory Crohn's disease, improvement in quality of life, and maintenance of remission in these patients. The efficacy of etanercept in CD, however, has not been demonstrated [25].

On the other hand, a 2007 meta-analysis indicated that all of the anti-TNF alpha agents then available (adalimumab, etanercept, and infliximab) were similar in efficacy in patients with AS [35], with respect to the patient global and pain assessment, the functional assessment, and the degree of inflammation as assessed by morning stiffness. The responses are typically rapid and appear to be durable. Patients who do not respond to or do not tolerate one anti-TNF agent may respond to an alternate anti-TNF agent [36].

Despite their efficacy, the indiscriminate use of anti-TNF-alpha drugs is discouraged because of cost concerns and a lack of long-term safety data [37]. They should be used primarily in Crohn's disease patients refractory to standard therapy, in order to help taper patients off steroids and transition them to effective long-term maintenance therapy using biological agents plus 6-MP or azathioprine, or in AS patients with active disease, as indicated by both the Bath ankylosing spondylitis disease activity Index (BASDAI) score and a physician global assessment, and failure of previous treatments. A BASDAI score of  $\geq 4$  is indicative of active disease that warrants consideration of anti-TNF therapy, but this criterion was not met in the mentioned case [18] [38].

Although the theoretic concept regarding the favorable influence of all these anti-inflammatory/disease-modifying agents on the associated gut inflammation exists, there is a striking paucity of controlled trials regarding this issue. Moreover, in spite of improvements in parameters of inflammation, the radiographic progression of AS patients seems not significantly be influenced by the biologic therapy [39].

Therefore, as biologic agents should be used only in patients with active articular disease, or when the intestinal inflammation is not responsive to other treatment modalities, it seems that there is no place at this moment for these drugs in the treatment of our patient. The problem is that the chronic ileal inflammation detected on his ileum predicts that the patient will have an aggressive form of SpA, and this might represent an indication for early intervention with aggressive therapy. Our opinion, however, is that we should wait for the disease to become more active, and for the failure

of less aggressive therapeutic approaches in order to initiate anti-TNF-alpha agents, and probably etanercept is not a choice in this case.

### CONCLUSIONS

This case report is important as a reminder that there is a wide differential diagnosis for granulomatous ileitis, even though the vast majority of such cases will be associated with Crohn's disease.

The case also illustrates the strong association between SpAs and IBD. The relationship between the two diseases is of particular interest to research workers, recent studies sustaining the hypothesis of a common immune-mediated inflammatory disease

pathway. There is emerging evidence that ileitis of spondyloarthritis might represent subclinical Crohn's disease.

There is rationale for carrying out ileocolonoscopy on patients with ankylosing spondylitis and abdominal symptoms as the ileal inflammation could give prognostic information and could guide treatment. Fecal calprotectin level could be used to stratify the need for evaluation of the bowel in patients with seronegative SpAs.

NSAIDs should be used with caution in this subset of patients, due to the inconsistent evidence of exacerbation of intestinal inflammation.

It is not clear at this point if more aggressive therapy should be initiated early in the course of this patient in order to prevent progression to a full IBD phenotype, since there is a paucity of data in the literature regarding this issue.

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*Un pacient de 27 ani având un istoric de 2 ani de spondilită anchilozantă se prezintă pentru evaluarea unui sindrom diareic intermitent, descoperindu-se afectare inflamatorie granulomatoasă la nivelul ileonului terminal. Diagnosticul diferențial, similaritățile în alterările imunologice din spondilita anchilozantă și boala Crohn, precum și opțiunile de tratament sunt discutate în această lucrare.*

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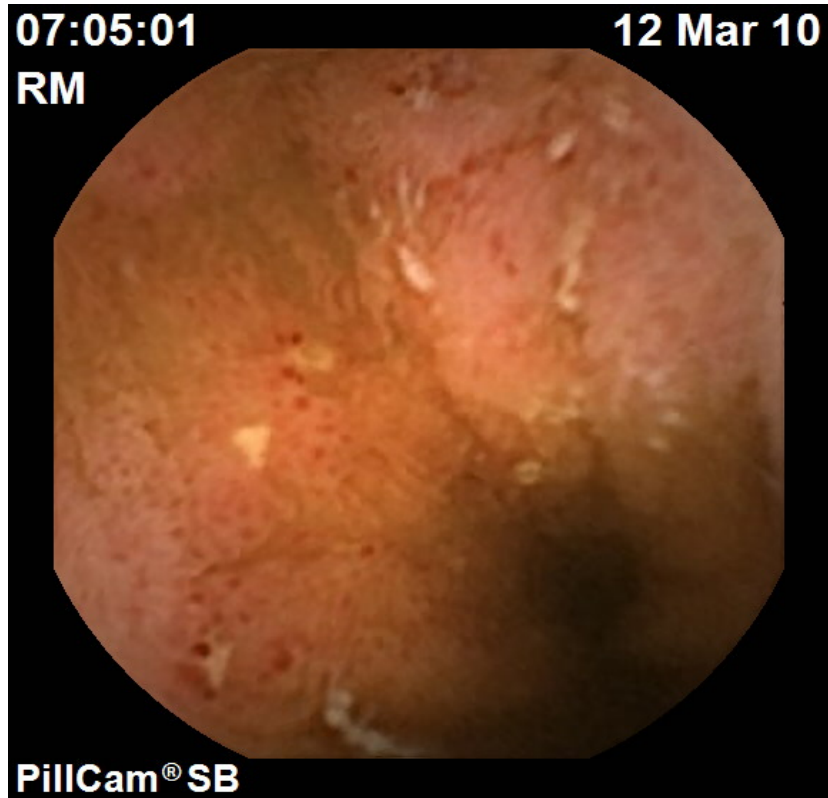


Fig. 1. – Area of mucosal edema and erythema, comprising also several petechiae and small aphthous ulcerations, located in the terminal ileum, as seen on capsule endoscopy examination.

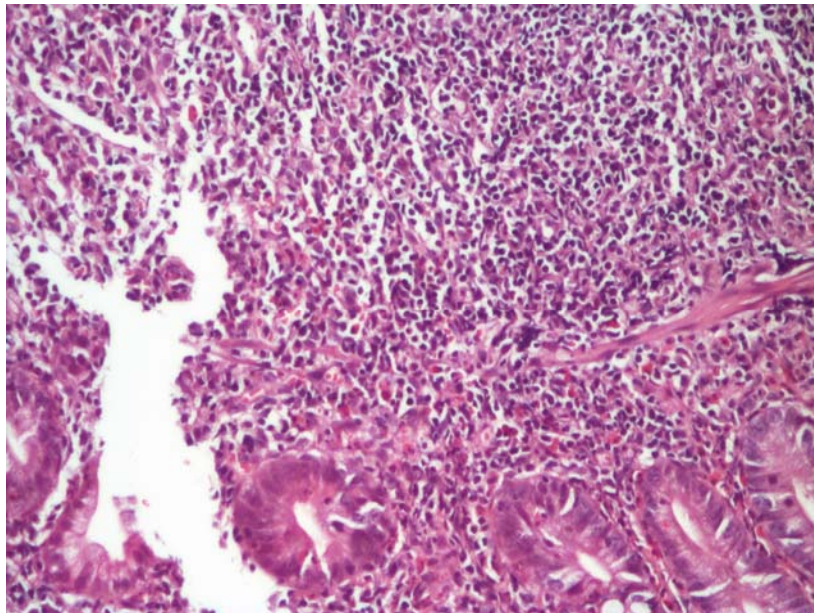


Fig. 2. – Section from an ileal biopsy revealing mixed inflammatory cells that involve the mucosa, muscularis mucosae and submucosa, with a fissure extending from the base of an aphthous ulcer to the submucosa, and a granuloma in the submucosal layer. Hematoxylin-eosin  $\times 100$ .