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Paradoxical Crohn's disease – myth or reality?

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ABSTRACT

We report the clinical case of an emergent Crohn's disease (CD) as a paradoxical effect after 24 months of successfully treatment with etanercept for active ankylosing spondylitis in a young women. Despite rapid and sustained response of articular disease (remission achieved as soon as three months and maintained through the entire period of administration), new onset intestinal manifestations developed during biological therapy. A complex assessment comprising clinical, endoscopic and histopathologic evaluation, associated with high levels of fecal calprotectin confirmed drug-induced inflammatory bowel disease (IBD) compatible with CD. Although optimal treatment strategy is not yet validated, discontinuation of putative etanercept and cycling to a monoclonal anti-TNF antibody (adalimumab) demonstrated positive outcomes for both articular and IBD.
New onset CD may be considered as an immune-mediated injury induced etanercept and should be considered in any patient with spondylarthritis in whom IBD develops with a clear temporal relationship with TNF inhibitors, especially etanercept.

Keywords: paradoxical inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, TNF antagonists, etanercept

INTRODUCTION

Biological therapies, especially agents targeting TNFa, are widely utilized in a variety of immune-mediated inflammatory rheumatic (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis) and non-rheumatic (psoriasis, inflammatory bowel disease [IBD], uveitis) conditions and are associated with rapid and sustained significant clinical response in long-term administration (1-3).

Although all TNF antagonists, either monoclonal anti-TNF antibodies or receptor-fusion protein, have comparable efficacy in musculoskeletal pathologies, differences in their molecular structure, mechanisms of action, as well as pharmacokinetic profile could explain not only specific immunomodulatory potency and different efficacy in treating uveitis and inflammatory bowel disease (IBD), but also differences in the toxicity profile (1-3).

Thus, anti-TNF agents may be responsible for the development of different paradoxical adverse events, meaning either new-onset or worsening of preexistent diseases similar to those they are used to treat, such as psoriasis, IBD, even anterior uveitis (3-5).

Etanercept has no demonstrated efficacy in IBD and is particularly involved in paradoxical granulomatous intestinal reactions (3,5-7). New onset Crohn's disease may be considered as an immune-mediated injury induced etanercept and should be considered in any patient with spondylarthritis in whom IBD develops with a clear temporal relationship with TNF inhibitors, especially etanercept (1,3,5-7).

We describe the development of an emergent Crohn's disease as a paradoxical effect during successfully treatment with etanercept for active ankylosing spondylitis in a young women, emphasizing the importance of pertinent assessment of gastrointestinal symptoms in patients on biological therapy with anti-TNF drugs.

CASE REPORT

We present the case of a 30 years-old women known with ankylosing spondylitis (1987 modified

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New York diagnostic criteria) treated with TNF antagonists (etanercept) in the last two years. She had no family history of spondylarthritis, as well as no personal history of enthesitis, peripheral arthritis, psoriasis, uveitis, or inflammatory bowel disease.

Etanercept was recommended in March 2014 for highly active disease (ASDAS-CRP 4.1, BASDAI 6.8), with significant disability and impaired quality of life (BASFI 6.5) and multiple negative prognostic factors (young patient, high levels of acute phase reactants, x-ray damage) as well. Rapid and dramatic improvement in disease activity, with a ΔASDAS-CRP of -2.9 points, was reported after the first three months of therapy; remission (ASDAS-CRP 1.2) was further maintained stable throughout the entire period of follow-up (Table 1, Fig. 1).

In October 2016, patient returned to the outpatient rheumatology department with a quiescent rheumatic symptomatology; in turn, she described new onset insidious and persistent intestinal manifestations comprising diffuse abdominal pain accompanied by diarrhea and rectal bleeding, in the absence of any apparent precipitating factor (food or infection). Etanercept was discontinued and patient addressed in the gastroenterology department for further assessment; since consistent improvement of intestinal symptoms was reported once the TNF antagonist was discontinued, and a simple rectoscopy performed revealed active hemorrhoidal disease, no other tests were proposed at that time point.

After a free-drug interval, biological therapy was restarted in late December same year due to a flare (clinical, biological) of axial disease; despite significant improvement of rheumatic condition, a relapse of the intestinal pathology with diffuse abdominal pain and diarrhoea (3-4/day) was the main reason to discontinue again treatment with etanercept. Fecal calprotectin evaluation showed abnormal increased values (1,290 mg/kg, normal values <50 mg/kg) raising the suspicion of *de novo,* etanercept-induced IBD.

TABLE 1. *AS parameters before and during Etanercept therapy*

AREAS	INSTRUMENTS	BEFORE INITIATION ETANERCEPT	TO 3 MONTHS	TO 6 MONTHS	TO 12 MONTHS
DISEASE	ASDAS-CRP	4.1	1.2	0.9	0.7
ACTIVITY	BASDAI	6.8	2.2	1.2	0.2
FUNCTION	BASFI	6.5	1	0.5	0.5
PAIN	VAS 0-10	8	1	0.5	0.5
MOBILITY	BASMI	1	1	1	1
PERIPHERAL JOINT	SJN 44	0	0	0	0
ENTHESITIS-MASES	13	0	0	0	0
ACUTE PHASE REACTION	CRP mg/l	27	4.3	2.7	1.9

Legend: ASDAS Ankylosing Spondylitis Disease Activity Score, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, BASFI Bath Ankylosing Spondylitis Functional Index, BASMI Bath Ankylosing Spondylitis Metrology Index, CRP C reactive protein, SJN Swollen Joint Number, VAS Visual Analoque Scale

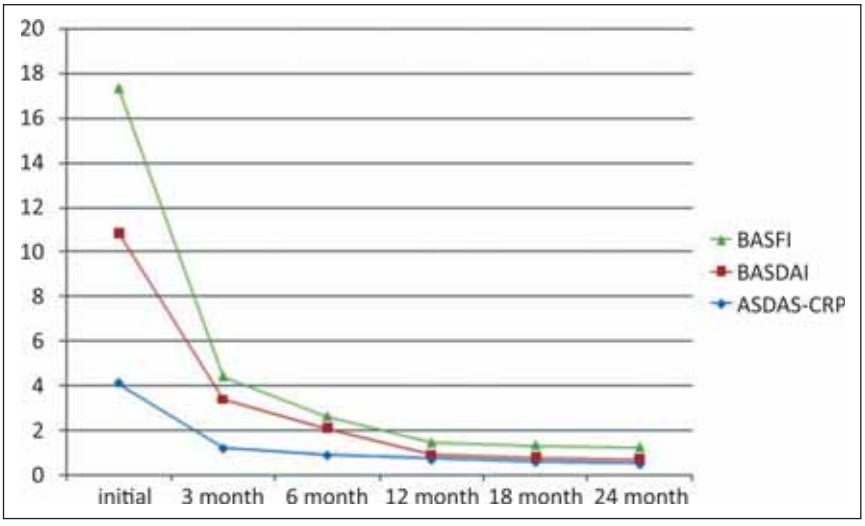

FIGURE 1. *Therapeutic response during Etanercept treatment*

Legend: *ASDAS Ankylosing Spondylitis Disease Activity Score, BASDAI Bath Ankylosing Spondylitis Disease Activity Index, BASFI Bath Ankylosing Spondylitis Functional Index, BASMI Bath Ankylosing Spondylitis Metrology Index, CRP C reactive protein*

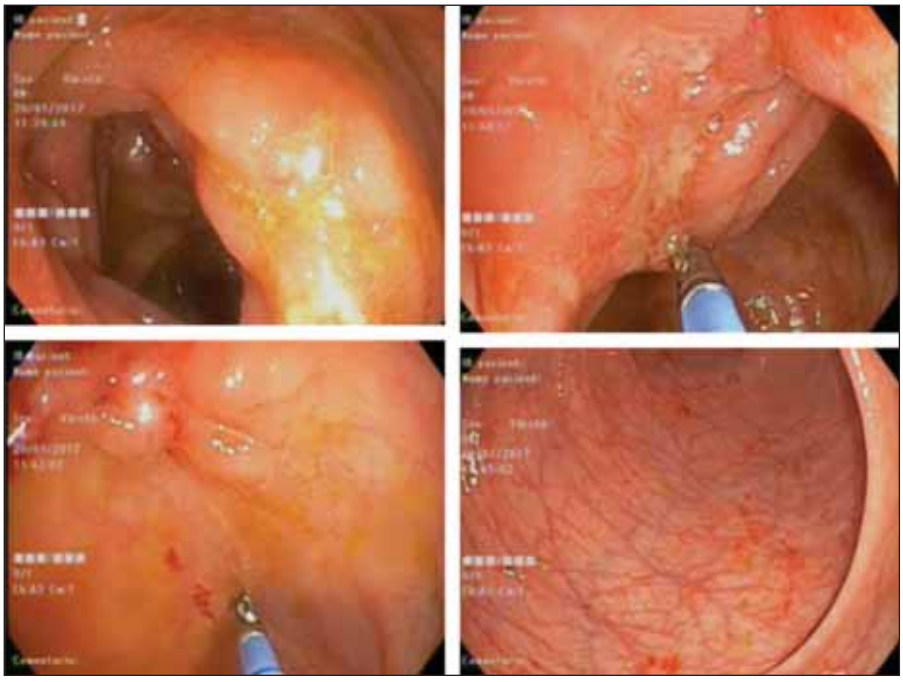

FIGURE 2. *Colonoscopy (typical CD images)*

An endoscopic evaluation (colonoscopy) with further histological assessment is essential for the diagnosis of IBD based on extent and severity of mucosal disease; in our patient colonoscopy detected rare aphthous colonic ulcerations accompanied by ileocecal inflammation and extensive ulcerations suggestive of Crohn's disease (Fig. 2).

At this point we advanced two main hypothesis, as follows: either we are face to a Crohn's disease induced by etanercept (direct relationship between drug administration and digestive manifestations), or AS was just an extra-intestinal manifestation of Crohn's disease.

Etanercept was replaced with another TNF inhibitor (adalimumab, 40 mg at two weeks interval), with positive outcomes on both articular and intestinal domains soon after initiation.

DISCUSSION

We reported the case of a paradoxical Crohn's disease induced by etanercept after 24 months of successful treatment outcomes in a young female diagnosed with AS.

A complex assessment was performed in our patient, following the classical diagnostic algorithm for IBD; no clinical, endoscopic or histopathologic differences were identified as compared to primary IBD. Moreover, high levels of fecal calprotectin detected as a first approach of the intestinal symptoms confirmed organic bowel disease suggesting further evaluation with more invasive procedures. Specifically, clinical manifestations declined during etanercept-free interval without any other immunosuppressive agent, while renewal of drug administration caused a new intestinal flare.

We are in front of a paradoxical effect associated with anti-TNF administration based on the following items: development of disease during etanercept therapy, relapse of clinical symptoms once the drug was restarted, positive outcomes with adalimumab replacing etanercept.

To summarize, this case underlines the importance of a correct evaluation of any new gastrointestinal symptom in patients receiving TNF inhibitors, particularly in those with a diagnosis of AS or other related disease, in order to find out whether we talk about a new onset or an exacerbation of an underlying inflammatory bowel disease.

We will further focus on different aspects of paradoxical IBD induced by TNF antagonists with particular relevance for daily practice.

Acknowledged as an adverse event related to the administration of TNF inhibitors aiming to control active rheumatic disease, paradoxical IBD is a rare condition, reported mainly in patients with spondylarthropathies, occurring particularly with etanercept and rarely with adalimumab, golimumab and infliximab, with a clear temporal relation (1-3).

Pathobiology of paradoxical IBD

The pathobiology of paradoxical IBD is still obscure; however, it is widely accepted that TNF blocking therapy is responsible for a local cytokine imbalance with high interferon levels in the intestinal microenvironment, promoting IBD-like histopathological and clinical features in a genetically predisposed host (carriers of genetic variants NOD2/CARD15) (4-7).

FDA approved TNF antagonists, classified in monoclonal anti-TNF antibodies (infliximab, adalimumab, golimumab, certolizumab) and the receptor-fusion protein (etanercept), have dissimilar molecular structures, and, subsequently, their biological activities and safety profile slightly differ. Although all five anti-TNF drugs are equivalent in controlling articular disease, their ability to influence IBD is not the same: only monoclonal antibodies have immunomodulatory potential and, thus, validated efficacy (3,8).

A closer look to the molecular structure and mechanisms of action of TNF inhibitors could explain why etanercept is the only one that has not shown any efficacy in IBD, and, moreover, is related to paradoxical gastrointestinal reactions (3,4).

Thus, etanercept specifically binds to TNF-α and lymphotoxin and its complexes with TNFα are less stable, with subsequent release of TNF (4,8); besides, this drug may enhance circulating T cells, promoting the synthesis of pro-inflammatory cytokines such as TNF-α and IFN-γ, which, in turn, are able to modulate intestinal inflammatory events, further IFN-γ production, and granuloma formation, as well (1,8,9).

On the other hand, abnormal macrophage function may account, at least in part, for Crohn's related intestinal inflammation, based on impaired secretion of TNFα by dysfunctional macrophages. In addition, a decreased in local TNFa-activity following the administration of certain biologics such as etanercept could trigger paradoxical IBD-like symptoms (3,10).

Interestingly, a two-step pathobiological process was described, with a rapid and intense TNF decline induced by drug initiation (step 1), followed by a chronic persistent modification in T cells potentially reversible with drug discontinuation (step 2) (4,7-9). Supplementary, only monoclonal antibodies are responsible for a significant T cells apoptosis (both circulating and lamina propria lymphocytes), based on direct binding to transmembrane TNF and by caspase 3 activation (3,4,7-9).

Pattern of paradoxical IBD

Inflammatory bowel disease as a paradoxical reaction associated with TNF inhibitors was reported with a temporal relationship, typically for etanercept (1,3,7); however, rare cases were described with monoclonal anti-TNF antibodies – adalimumab (7, 11), golimumab (12,13), even, infliximab (7).

Two main clinical settings are documented, comprising (i) paradoxical IBD induced by anti-TNF agents administered to control disease activity in patients with inflammatory immune-mediated rheumatic disorders, particularly spondylarthropathies; and (ii) relapse of the paradoxical lesion when restarting the putative drug (3,7). In addition, it was also assumed that TNF antagonists could reveal a pre-existing subclinical inflammatory intestinal condition (7,14).

Interestingly, the history of IBD enhances tenfold the relative risk of reactivation with etanercept, without any influence for infliximab-treated patients (1,3).

Generally, there are no clinical, endoscopic and histopathological variances between classical and paradoxical IBD. Furthermore, at least four subtypes of anti-TNF induced-IBD are recognized, comprising Crohn's disease (up to 50%) and Crohn's-like disease (atypical histopathological pattern with endoscopic findings and an extension suggestive of the disease) (around 44%), ulcerative colitis (6%) and indeterminate colitis (3,7).

Time after initiation of etanercept to onset of the IBD paradoxical reaction varies largely, regularly a few months (1,3,7).

Also, paradoxical IBD is characteristically reported in patients diagnosed with spondylarthritis including AS, juvenile idiopathic arthritis, and rarely in psoriatic arthritis (3,4,7,15)

Management of paradoxical IBD

There is no validated therapeutic algorithm for paradoxical IBD. However, several strategies have been proposed, mainly depending on the IBD subtype, the background of csDMARD and/or glucocorticoids. Thus, we can discuss the following protocols: (i) discontinuation of the responsible biological agent, commonly etanercept; paradoxical intestinal symptoms usually disappear, but re-occur if the tentative to reintroduce etanercept; (ii) cycling to a second anti-TNF monoclonal antibody, infliximab or adalimumab, with subsequent improvement of the paradoxical condition and without relapses during evolution (3,4,7).

Moreover, if a paradoxical ulcerative colitis developed in a patient receiving etanercept combined with a remissive drug, the decision to withdrawal the TNF receptor is mandatory and sufficient to improve intestinal status; conversely, if the paradoxical event emerged under monotherapy with etanercept, stopping the biological and addition of azathioprine and corticosteroids may represent a beneficial option (1,3).

Finally, a quite infrequent situation is to add mesalazine or sulfasalazine, while preserving etanercept in the therapeutic regimen (1,3).

CONCLUSIONS

Key learnings for routine practice include:

- all patients with AS under etanercept developing any new gastrointestinal symptom could be considered as new onset IBD (particularly Crohn‘s disease);
- it might be appropriate to check if there are subclinical intestinal lesions in patients with spondylarthropaties before initiating etanercept;
- fecal calprotectin shows sufficient accuracy to differentiate symptomatic patients with organic bowel disease, e.g. IBD from those with functional disease, e.g. irritable bowel syndrome;
- several rheumatic (AS, juvenile idiopathic arthritis) and non-rheumatic (psoriasis) immune mediated conditions benefit from any of anti-TNF agents (including etanercept), while others including Crohn‘s disease and uveitis have proven benefit only from monoclonal antibodies such as infliximab and adalimumab.

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