ABSTRACT: Background: In patients with autoimmune diseases like inflammatory bowel diseases there has been reported a drug-induced lupus like syndrome secondary to TNFα inhibitors. Objective: clinical case presentation and literature review of patients who develop lupus-like syndrome in relation to TNFα antagonists and their future therapeutic options. Materials and methods: we report the case of a 27-year old woman with colonic Crohn's disease on combo-therapy (infliximab+azathioprine) for nearly two years who developed peripheral arthritis and malar rash in the context of TAILS. Results: our patient had positive anti-nuclear antibody, arthritis, malar rash, anemia and leukopenia. Her symptoms remitted after discontinuation of infliximab and subsequently she started adalimumab for her Crohn's colitis; more than a year after switching between TNFα inhibitor molecules and stopping azathioprine she is feeling very well. TAILS is a rare condition described in the literature that can affect 0.5-1% of individuals, more often in association with etanercept and infliximab. Several pathogenic routes have been incriminated in the apparition of this syndrome there is still no definite mechanism up to date. Management options include discontinuation of the drug, corticosteroids, hydroxychloroquine sulfate and switching for other immunosupressives. Conclusions: TAILS can appear even a long time after first exposure to TNFα antagonists. In our case, the association with azathioprine was not a primary prophylactic solution.

KEYWORDS: TAILS, lupus-like syndrome, IBD, TNFα inhibitors

Introduction

Inflammatory bowel diseases (IBD) are chronic immune mediated inflammatory diseases of the digestive tract. IBDs involve a complex interaction among genetic, altered physiology, microbiology and immunology [1-3]. They can be multisystemic and affect any part of the bowel with complications to the skin, eyes, joints, kidneys and liver or IBDs can be strictly limited to the colonic mucosa like the ulcerative colitis (UC) [4]. Crohn's disease (CD) is typically transmural and because it affects all the layers of the bowel can lead to stenoses and fistulae. Tumor necrosis factor alpha (TNFα) is a pro-inflammatory cytokine implicated in the pathogenesis of several autoimmune diseases [5]. TNFα antagonists were developed in the '90s and have shown very good results in controlling the inflammatory process of active IBDs. However, blocking the physiologic effects of this cytokine can lead to adverse effects [6]. Three agents, including infliximab (a chimeric monoclonal antibody), etanercept (a soluble receptor fusion protein) and adalimumab (a human monoclonal antibody) have been reported to cause a syndrome called drug-induced lupus-like syndrome (DILS) [7-9]. We will further refer to this diagnosis more specifically as TNF alpha antagonist-induced lupus-like syndrome (TAILS). In our country a new molecule has been recently approved for the management of IBD: golimumab (a human monoclonal antibody) and FDA has approved several years ago certolizumab pegol (a pegylated humanized Fab antibody fragment).

Case Report

A 27 year old woman with IBD, phenotype CD A2L2B1 (Vienna classification) [10], presented with malar rash and arthritis nearly 2 years after the initiation of infliximab therapy for her underlying disease. She had successfully been treated with 5ASA (aminosalicilic-acid) from 2007 to 2010. In 2010 she had 2 severe flaires of disease activity treated with corticosteroids (CS) and after the first we initiated immunosupression with azathioprine. Since the second flaire appeared 3-4 months after starting azathioprine and was associated with erithema nodosum, we considered she was resistant to immunosupresors and decided it was time for TNFα inhibitors. In December 2012 the osteoarticular manifestations started: she had non-erosive arthritis in the metacarpofalangean joints, without arthicular deformations (Fig.1), that was starting about 2 weeks after infliximab application and accentuated until the moment of the next application (peripheral spondyloarthritis?) [11-14].
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In February 2013 the laboratory investigation revealed mild anemia and low white blood cell count, C-reactive protein slightly elevated, normal blood urea nitrogen and creatinine. The ileocolonoscopy was normal, so was the Quantiferon TB-gold test; two months after she developed malar and photosensitive rash (Fig.2 and 3). We decided to perform a more thorough workup: uncertain antibodies to double stranded DNA (21.5 UI/ml), positive antinuclear antibody (1:1280), positive antihistone antibody (120 U/ml). Normal ECG and chest X-ray.

Correlation of the clinical exam and laboratory results in the context of a patient receiving TNFα antagonists established the diagnosis of infliximab induced TAILS with 4 of the criteria for systemic lupus [15]. Treatment consisted of systemic corticosteroids and infliximab was discontinued. The patient was transitioned to subcutaneous injections of adalimumab, once every two weeks, that successfully controled her CD and azathioprine was rapidly discontinued as well. The skin and joint involvement resolved completely within a couple of months and she is now, 18 months later, in endoscopic remission of the underlying disease and TAILS never recurred.

Discussion

Epidemiology and clinical characteristics

TAILS is a very rare condition. A recent paper analysed the French pharmacovigilance database between 2000 and 2012 confirmed 39 cases from 309671 spontaneous reports. The authors found a decreased risk with etanercept compared with monoclonal TNFα inhibitors (infliximab and adalimumab) [16]. This results are inconsistent with the previous data that found adalimumab to be the least prone to inducing TAILS [17]. Rheumatoid arthritis and CD are the two most commonly autoimmune diseases associated with this syndrome and there is a
2:1 risk for women compared with men for drug induced lupus-like syndrome [16]. The mean age of onset ranges between 45 and 51 years [8]. TAILS is a lupus-like syndrome that occurs after exposure to TNFα inhibitors and resolves after discontinuation of the incriminated agent. There are three variants of TAILS, like idiopathic lupus: drug-induced systemic lupus erythematosus (SLE), drug induced subacute cutaneous lupus and chronic cutaneous lupus. There are no specific diagnostic criteria, but the least rigorous requires one or more symptoms compatible with lupus erythematosus, no previous history of lupus, active exposure to a drug known to cause DILS and resolution of symptoms when the incriminated drug in discontinued [18]. Our patient had the SLE variant and met 4 of the 11 American Congress of Rheumatology diagnostic criteria for idiopathic SLE [15]. The most common clinical manifestations are those localised to the skin: maculopapular rash, malar rash, photosensitivity and alopecia. Non-cutaneous manifestations include arthritis, serositis, myositis, hematological (anemia and leukopenia) renal and neurological disorders. Costa MF et al estimated that 72% of patients with TAILS have skin manifestations [19]. When skin lesions are biopsied the pathological changes are similar to those with idiopathic SLE.

**Laboratory investigations**

Patients are normally screened for laboratory abnormalities found in idiopathic SLE. Positive antinuclear antibodies range from 79-100%. Anti-dsDNA antibodies are found in 72-92%. Anti-phospholipid antibodies have been found in 11-50% of the patients with TAILS [17]. Anti-histone antibodies are often incriminated in other DILS but frequently in TAILS. Other antibodies include anti-SSA/Ro, anti SSB/La, anti RNP and anti-Smith. Hypocomplementemia is found in up to 59% of patients [19]. Cytopenias are the most common hematological disorders. Renal involvement is rare but nevertheless a urine analysis should be performed in each suspected patient to exclude severe renal dysfunction.

**Pathogenesis**

There are several patogenic hypotheses: TNFα is inducing apoptosis in inflammatory cells. This process releases antigenic particles which stimulate the production of auto-antibodies in susceptible individuals [9]. The second hypothesis has in center the increased risk of infections secondary to the relative immunosupression of TNFα inhibitors. This activates polyclonal B lymphocites and auto-antibodies [20].

The third hypothesis is that the TNFα antagonists promote humoral autoimmunity and by that favours T-helper 2 responses while supressing T-helper 1 responses. This in time leads to a decreased number of cytotoxic T lymphocytes needed to destroy autoreactive B lymphocytes [19].

The most recent hypothesis is that the rate of clearance of dead cells, increased number of plasmacytoid dendritic cells, along with decreased levels of TNFα may influence who will develop autoimmunity and eventually lupus, after treatment with TNFα inhibitors [21].

**Prevention**

There are no recommendations for prevention of TAILS. However, the development of anti-nuclear antibodies and anti-dsDNA may predict the individuals who will develop TAILS. Concurrent use of other immunosuppressors might reduce the rate of autoantibody production and potentially decrease the risk of developing this syndrome but, like our case highlights, there is no significant risk reduction in those patients.

**Treatment**

The first measure is to stop the offending drug. In nearly all cases this leads to resolution of symptoms. This is sustained by a decrease in the levels of auto-antibodies. Severe cases require additional management to fully resolve their symptoms; this additional measures require corticosteroid administration orally or intravenously, immunosuppressives like azathioprine and cyclophosphamide, methotrexate or mycophenolate [22]. Our patient received corticosteroids and infliximab was discontinued. Some studies have sugested that mild symptoms or patients with only positive auto-antibodies should be treated with optional drug cessation [22]. The most important question that TAILS poses is whether to switch to another anti TNFα agent and if that change in the management leads to recurence of the same adverse events. The majority of studies show that switching between TNFα inhibitors is safe [8]. There are also studies which support re-challenging with the same agent that initially caused TAILS but this data should be interpreted cautiously [23].

Our patient tolerated well infliximab in combination with azathioprine for controlling her CD. Nearly two years after induction of TNFα inhibitor she developed TAILS so we were
forced to stop this treatment. After switching to adalimumab, the other anti TNFα agent approved at that time for CD, in our country, she remained in remission without recurrence of TAILS. Now, more than 18 months from TAILS resolution, we just found out that she is waiting for her first baby which seems to be in very good form.

Conclusions

Our case is particular because TAILS developed more than a year after first exposure to TNFα inhibitors that was given in association with another immunosupressor (azathioprine). She had systemic lupus-like syndrome that required a short course of corticosteroids and that evolved favorably after 18 months from switching to another monoclonal antibody, adalimumab.

References


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