Clinical Case Study

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Infliximab-Induced Lupus: A Case Report

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Key Words

Infliximab, therapeutic use · Inflammatory bowel diseases, drug therapy · Lupus erythematosus, systemic/chemically induced · Tumor necrosis factor alpha, therapeutic use

Abstract

We report the case of a 48-year-old, leukodermic female diagnosed with ulcerative proctitis for 4 years and latent tuberculosis. She was allergic to salicylates and had a minor allergic reaction to infliximab (rash, vertigo, and headache). Thereafter, she started azathioprine (2.5 mg/kg/day). She maintained intravenous infliximab, together with prophylaxis with clemastine and hydrocortisone, due to the steroid-dependent proctitis. The therapy was continued every 8 weeks with anti-tumor necrosis factor for about 3 years. The analytical evaluation when she was diagnosed with ulcerative proctitis (February 2011) showed negative antinuclear antibodies (ANA), double-stranded-DNA antibodies (anti-dsDNA), antineutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies, and a positive outer membrane protein antibody. About 2 years and 6 months after starting infliximab (November 2013), the patient complained of inflammatory symmetrical polyarthralgia (knee, shoulder, elbow, and wrist) without synovitis, which started every week before the administration of infliximab. Resolution of symptoms was observed after each infliximab infusion. In July 2014, the autoantibody re-evaluation showed positive ANA with a homogeneous pattern with a titer of 1:640, weak positive anti-dsDNA (30.2), and positive anti-histone with C3 decreased (80.3). She was then diagnosed with lupus induced by infliximab and initiated hydroxychloroquine 400 mg. Infliximab was suspended. On re-evaluation, the erythrocyte sedimentation rate was 25 mm/h (1st hour), C-reactive protein 0.5 mg/dL (previously erythrocyte sedimentation rate 15 mm/h and C-reactive protein 1.2 mg/dL), and endoscopically, the mucosa was scarred, with some atrophy and scarce mucus in the lower rectum. About 10 months after discontinuation of infliximab, repeated autoantibodies proved all negative, keeping only low C3 (87). The patient also reported complete resolution of the arthralgia.

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Lupus Induzido por Infliximab: Relato de um Caso

Palavras Chave
Doenças inflamatórias intestinais, tratamento · Factor de necrose tumoral alfa, uso terapêutico · Infliximab, uso terapêutico · Lupus eritematoso, sistémico/induzido quimicamente

Resumo
Relato do caso de uma mulher, 48 anos, leucodérmica, com o diagnóstico de proctite ulcerosa com 4 anos de evolução e tuberculose latente. Alérgica aos salicilatos e com reacção alérgica minor ao infliximab (rash, cefaleia e vertigem), iniciou azatioprina (2,5 mg/kg/dia) apenas após a reacção alérgica. Manteve infliximab com profilaxia endovenosa com clemastina e hidrocortisona dada a cortico-depedência da proctite. A terapêutica com anti-TNF foi mantida de 8 em 8 semanas durante cerca de 3 anos. Na avaliação analítica aquando o diagnóstico da doença inflamatória intestinal (Fev 2011) apresentava ANA, anti-dsDNA, ANCAs e ASCA negativos com anti-OMP positivo. Cerca de 2 anos e meio após o início de infliximab (Nov 2013), iniciou quadro de poliartralgia inflamatória simétrica (joelhos, ombros, cotovelos e punhos) sem sinovite com início regular na semana prévia à admnistração programada de infliximab e resolução após a infusão endovenosa. Em Julho de 2014, apresenta ANA positivos com padrão homogéneo com título de 1/640, anti-dsDNA equívoco (30.2), anti-histonas positivo com C3 diminuído (80.3). Foi diagnosticada com lupus eritematoso sistémico induzido por infliximab e iniciou hidroxicloroquina 400 mg. O infliximab foi suspenso. Na reavaliação da doença, destaca-se VS 25 mm/h (1ª hora), PCR 0,5 mg/dL (previamente VS 15 e PCR 0.6) e endoscopicamente mucosa cicatrizada, com alguma atrofia e escasso muco no recto baixo. Cerca de 10 meses após a suspensão do infliximab, repetiu auto-anticorpos que se revelaram todos negativos, mantendo apenas o C3 baixo (87). Verificou-se ainda resolução completa das queixas articulares.

Introduction

Tumor necrosis factor alpha blocker therapies (anti-TNF) are widely used in the treatment of inflammatory bowel disease (IBD) and in a rapidly expanding number of rheumatic and immune-mediated diseases. Its use has been associated with the development of anti-TNF antibodies, autoantibodies, and, paradoxically, with autoimmune diseases [1]. The induction of autoantibodies is frequent, but the development of an autoimmune disease such as drug-induced lupus (DIL) is a rare event [1, 2].

DIL is a clinical syndrome with features similar to systemic lupus erythematosus (SLE), but with some differences in laboratory and clinical findings [3–5]. The diagnosis of lupus-induced infliximab should be considered in a patient who develops antinuclear antibodies (ANA) and presents with at least 1 clinical criterion for lupus (arthritis, serositis, or rash) [5]. Concomitant immunosuppression is known to reduce autoantibody formation, and in most DIL cases, the suspension of anti-TNF leads to the resolution of the condition [2, 5]. In a large series of 72 cases of lupus induced by anti-TNF, the signs and symptoms resolved in 71 patients [6]. Some cases might require specific therapy while symptoms prevail [7]. The time to clear the autoantibodies is superior to the clinical remission and in some patients may take more than 1 year [8].

According to post-marketing studies, DIL has an estimated prevalence of 0.19–0.22% for infliximab, 0.18% for etanercept, and 0.10% for adalimumab. Nevertheless, in randomized controlled trials, the prevalence is higher, reaching 0.78% [7].

Clinical Findings

The subject of this report is a 48-year-old, leukodermic female born and resident in Funchal, Madeira Island. She was medicated with amiloride 5 mg plus hydrochlorothiazide 50 mg once daily for arterial hypertension. Five years ago, she had a left oophorectomy for an ovarian cyst. She was allergic to acetylsalicylic acid and ibuprofen. She denied alcohol consumption, tobacco, or drug abuse. No relevant family history was found.

In January 2011, the patient was referred to the gastroenterology department with a 2-month history of chronic diarrhea (4–5 soft stools per day). Three weeks before, rectal bleeding, urgency, and tenesmus had begun, and 1 week before, the passage of mucus had occurred.

A total colonoscopy with ileoscopy revealed a normal terminal ileum and colonic mucosa. In the rectum, up

to 15 cm from the anal margin, hyperemic mucosa with petechiae, great friability, and mucus was found. The endoscopic appearance was compatible with ulcerative proctitis Mayo endoscopic subscore 2. Histologically, the ileum had no abnormalities, and the rectum revealed distortion of the glandular architecture and mucin depletion with a chronic inflammatory process with signs of activity and ulceration. There were numerous crypt abscesses, and in the lamina propria, xanthomatous macrophages were negative for periodic acid-Schiff stain, periodic acid-Schiff diastase stain, and Ziehl-Neelsen stain.

The analytical evaluation at this time showed negative ANA, double-stranded-DNA antibodies (anti-dsDNA), perinuclear antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic-ANCA, and anti-*Saccharomyces cerevisiae* antibodies (ASCA, IgG, and IgA). There was a positive outer membrane protein antibody of 42.5 (reference range [RR] <20).

She was prescribed mesalazine 1 g suppositories once daily. Three days later, she developed an urticarial reaction, and mesalazine was suspended; the urticaria rapidly subsided. She was then started on budesonide 2 mg enemas once daily. Two months later, she maintained the symptoms and had more rectal bleeding. Prednisolone 40 mg o.s. daily was initiated, and within 10 days, rectal bleeding, urgency, tenesmus, or passage of mucus disappeared, but she maintained diarrhea (4 soft bowel movements per day). When prednisolone was weaned (at 10 mg/day), the symptoms relapsed, and we decided to introduce infliximab given that the patient was very symptomatic with an impaired quality of life that conditioned labor absence. The objective at this time was a fast response, and immunosuppressant was not added.

The pre-infliximab screening revealed latent tuberculosis, and the patient was administered isoniazid 300 mg per day and 20 mg pyridoxine for 6 months. One month later, she started infliximab treatment, which included prophylaxis with hydroxyzine 25 mg o.s. and intravenous (i.v.) prednisolone 75 mg. The undergoing treatment for latent tuberculosis was a major conditioning factor for an early top-down approach.

During the third infusion of infliximab, the patient complained of headache and vertigo, and a generalized rash was objectified. She was immediately medicated with metoclopramide i.v. and 80 mg of methylprednisolone i.v., with clinical improvement. The option of monotherapy with infliximab was upgraded at this time (about 10 weeks of treatment with isoniazid) to combined immunosuppression with anti-TNF and an immunosuppressant (accelerated step-care approach). Therefore, azathioprine at 150 mg per day (2.5 mg/kg) was added with the objective of reducing anti-infliximab antibody formation, weighing carefully against the risk of a tuberculosis reactivation. In view of the steroid-dependent colitis, it was decided to maintain infliximab therapy along with prophylaxis with clemastine 2 mg i.v. and hydrocortisone 300 mg i.v. No allergic reactions were observed during the following 3 years of therapy.

Six months after the initiation of infliximab, the sigmoidoscopy revealed abundant mucus, loss of the vascular pattern, and a slight friable mucosa in the last 15 cm of the rectum (Mayo subscore 1).

Diagnostic Focus and Assessment

About 2 years and 6 months after starting infliximab (November 2013), the patient complained about malaise and inflammatory symmetrical polyarthralgia (knee, shoulder, elbow, and wrist) without objectifiable arthritis and with a regular start of the symptoms in the week prior to the scheduled administration of infliximab and resolution of the complaints after the i.v. infusion.

In July 2014, the autoantibody re-evaluation showed a positive ANA with a homogeneous pattern and a titer of 1:640, weak positive anti-dsDNA (30.2; RR <20), positive anti-histone, low C3 (80.3), and IgM 281 mg/dL (RR 40–230). The patient was diagnosed with lupus induced by infliximab, and infliximab was suspended. Anti-infliximab antibodies were not available at this time in our hospital. The remaining investigation revealed a normal renal function (estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] of 104 mL/min/1.73 m^2) without any change in urinary sediment analysis (including proteinuria and hematuria). There were no signs of serositis, oral ulcers, photosensitivity, blood disorders (leukopenia, lymphopenia, thrombocytopenia, or hemolytic anemia), neurologic disorder, or rash (malar or discoid). The clinical presentation was not compatible with other pathologies presenting with symmetrical polyarthralgia because of the specified time frame of its presentation. In fact, the patient denied other symptoms suggestive of rheumatoid arthritis (early morning joint stiffness, synovitis of metacarpophalangeal joints, proximal interphalangeal or wrist joints, and subcutaneous nodules) or seronegative arthritis, including IBD-associated arthritis (mainly asymmetrical, large joint oligoarticular involvement; possible spinal involvement).

On re-evaluation of ulcerative proctitis at the time of suspension, the erythrocyte sedimentation rate was 25 mm/h (first hour), C-reactive protein was 0.5 mg/dL, and endoscopically, a scarred mucosa with some atrophy and scarce mucus in the lower rectum was found. In a total colonoscopy, no other abnormalities were detected.

Therapeutic Focus and Assessment

Following the diagnosis of infliximab-induced lupus, the patient suspended infliximab and started hydroxychloroquine 400 mg daily. After 8 weeks, she experienced total remission of the symptoms.

About 10 months after the discontinuation of infliximab, the autoantibodies that were previously positive (ANA, anti-dsDNA, and anti-histone) were repeated and proved all negative, keeping only a low C3 (87). She also reported complete resolution of arthralgia and malaise. Hydroxychloroquine and azathioprine were maintained.

One year after the suspension of infliximab, the sigmoidoscopy was repeated, showing a healed mucosa with some atrophy and scarce mucus in the lower rectum.

Follow-Up and Outcomes

One year and 6 months after the suspension of infliximab, the patient remains asymptomatic and shows no abnormalities in the blood tests (complete blood count, erythrocyte sedimentation rate, and C-reactive protein).

Discussion

According to the SLICC criteria [9], the patient fulfilled 3 immunological criteria for SLE that appeared after therapy with infliximab: high ANA, high anti-dsDNA, and reduced C3. The patient complained of polyarthralgia, but this was not objectified as polyarthritis and therefore not accomplishing the minimum of 1 clinical criterion according to this classification. However, the SLICC criteria are established for the diagnosis of SLE, and no specific criteria or tests exist to establish the diagnosis of DIL, which has some distinguishing features, as previously stated. This is typically diagnosed in a patient taking a drug associated with DIL for at least 1 month and who presents with at least 1 clinical feature characteristic of SLE and a positive ANA [4]. Our patient reported malaise and polyarthralgia 2.5 years after taking infliximab and fulfilled 3 immunological criteria. A spontaneous resolution of the clinical picture typically occurs within weeks and contributes to confirm the diagnosis [4]. In our case, the clinical remission was verified 8 weeks after the suspension, and the immunological remission 9 months thereafter, strongly supporting the definitive diagnosis of infliximab-induced lupus.

The frequency, clinical, and serological characteristics of anti-TNF-induced lupus differ from classical DIL. The clinical presentation is characterized by arthralgia or polyarthritis, mucocutaneous manifestations, and, less frequently, serositis. Renal and neurological manifestations are extremely rare. The most frequent antibodies are ANA and anti-dsDNA, positive in 79 and 72% of the cases, respectively. Anti-histone antibodies, a hallmark of DIL (procainamide or hydralazine), were only positive in 17–57% of the patients [6, 10].

Treating 500 patients with infliximab and following them up for 17 months the Mayo clinic reported only 3 DIL cases [11]. Older patients and dsDNA antibody levels ≥9 U/mL (but not ANA titers ≥1:240) are risk factors for the development of ANA and lupus, while concomitant immunosuppressive therapy may have a protective effect [12].

Due to the significant number of reported cases of adalimumab-induced lupus [10], we decided not to initiate another anti-TNF until a new flare occurred, maintaining hydroxychloroquine and azathioprine. In 54 reported cases of autoimmune diseases induced by anti-TNF, therapy reintroduction resulted in 69% relapses when the same biological was used and in 29% when starting another anti-TNF [10]. However, it is important to stress that the duration of the follow-up was not detailed, which can underestimate the data found. In the context of IBD, 8 patients were treated with a second anti-TNF agent, of whom 2 patients developed recurrent DIL following 3 months of therapy (25% relapse); the remaining patients remained well after a median follow-up of 5 months [13].

The experience with golimumab is still very limited compared to infliximab or adalimumab. There is a report of a subacute cutaneous lupus erythematosus exacerbation with golimumab [14]. To our knowledge, there are no cases of golimumab-induced lupus to date, and therefore, golimumab would be the authors' choice in case of a new flare of ulcerative colitis in the patient presented herein.

Statement of Ethics

The patient provided written consent for the publication of this case report. The CARE guidelines have been adopted for writing this case report [15].

Disclosure Statement

R.F. has served on a scientific advisory board for AbbVie (adalimumab). The remaining authors have no conflicts of interest to disclose.

References

1 Atzeni F, Talotta R, Salaffi F, Cassinotti A, Varisco V, Battellino M, et al: Immunogenicity and autoimmunity during anti-TNF therapy. Autoimmun Rev 2013;12:703.
2 De Bandt M: Lessons for lupus from tumour necrosis factor blockade. Lupus 2006;15:762.
3 Hess E: Drug-related lupus. N Engl J Med 1988;318:1460.
4 Borchers AT, Keen CL, Gershwin ME: Drug-induced lupus. Ann NY Acad Sci 2007;1108:166–182.
5 Araújo-Fernández S, Ahijón-Lana M, Isenberg DA: Drug-induced lupus: including anti-tumour necrosis factor and interferon induced. Lupus 2014;23:545–553.
6 De Bandt M, Sibilia J, Le Loët X, Prouzeau S, Fautrel B, Marcelli C, et al: Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7:545.
7 Ramos-Casals M, Roberto-Perez-Alvarez C, Cuadrado MJ, Khamashta MA: Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev 2010;9:188–193.
8 Wetter DA, Davis MD: Lupus-like syndrome attributable to anti-tumor necrosis factor alpha therapy in 14 patients during an 8-year period at Mayo Clinic. Mayo Clin Proc 2009;84:979–984.
9 Petri M, Orbai AM, Alarcon GS, et al: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–2686.
10 Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, et al: Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. Medicine (Baltimore) 2007;86:242.
11 Colombel JF, Loftus EV Jr, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, et al: The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. Gastroenterology 2004;126:19–31.
12 Beigel F, Schnitzler F, Paul Laubender R, Pfennig S, Weidinger M, Göke B, et al: Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF-α antibody-treated patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:91–98.
13 Subramanian S, Yajnik V, Sands BE, Cullen G, Korzenik JR: Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent. Inflamm Bowel Dis 2011;17:99–104.
14 Wilkerson E, Hazey MA, Bahrami S, Callen JP: Golimumab-exacerbated subacute cutaneous lupus erythematosus. Archiv Dermatol 2012;148:1186–1190.
15 Gagnier J, Kienle G, Altman DG, Moher D, Sox H, Riley DS; and the CARE group: The CARE guidelines: consensus-based clinical case report guideline development. J Clin Epidemiol 2014;67:46–51.