Etanercept-induced granulomatous hepatitis as a rare cause of abnormal liver tests

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Abstract

The authors report the case of a 76 year-old man with rheumatoid arthritis treated with prednisolone and etanercept. The patient was seen for persistent changes in liver tests lasting for six months, with a mixed pattern. The patient denied intake of new drugs or dietary/herbal supplements. Imaging studies showed mild steatosis. Additional study for chronic liver diseases only revealed positivity for anti-nuclear antibodies. Liver biopsy revealed noncaseating granulomas in some portal tracts. Consequent etiologic study for granulomatous diseases showed negative or normal results. So it was decided to suspend etanercept, with a subsequent gradual improvement on analytical parameters that normalized three months later. To date, only one case of granulomatous liver disease associated with an anti-TNF agent was described in the literature. This case also raises the question whether the development of granulomatous processes associated with anti-TNF agents has been underdiagnosed due to the presence of other concomitant immunosuppressant therapies. (Acta gastroenterol. belg., **2019**, 82, **93-95**).

Introduction

TNF-alpha inhibitors (anti-TNF) have proven efficacious in the treatment of several immune mediated diseases such as rheumatoid arthritis (RA), spondyloarthritis, inflammatory bowel disease (IBD) or psoriasis. The safety profile of anti-TNF agents as infliximab, etanercept, adalimumab or golimumab is mainly focused on the increased risk of infections, malignancies, demyelinating disorders, and cardiovascular diseases. Because TNF-alpha is a key cytokine involved in granuloma formation, TNF-α blockade, which suppresses granuloma formation, has been suggested as a potential treatment for granulomatous diseases, mostly sarcoidosis (1,2). However, it has been recently published paradoxical reports of new sarcoidosis-like diseases in patients receiving anti-TNF agents, mainly etanercept, affecting one or more organs, including the lungs, thyroid, kidneys and lymph nodes (3-7). The risk of hepatotoxicity associated with anti-TNF agents appears to be small, with less than 50 cases reported in the literature. Various types of hepatic involvement have been noted, including acute liver failure, hepatitis, and cholestasis. Until now, there is only one reported case of granulomatous hepatitis due to an anti-TNF agent, etanercept (8). We describe the second one in a RA patient also under etanercept treatment.

Case Report

The authors report the case of a 76 year-old man, partially autonomous for daily activities, to whom an erosive and seropositive RA was diagnosed in 1994. He had positivity for rheumatoid factor and anti-cyclic citrullinated peptide antibodies, without any extra-articular manifestations. He was previously treated with methotrexate and infliximab between 2001 and 2003 and he is under etanercept in monotherapy since 2003. The patient had also past medical history of chronic obstructive pulmonary disease GOLD stage II, recurrent angioedema, essential hypertension, cerebrovascular disease and glaucoma. His daily chronic medication included daily acetylsalicylic acid 150 mg, amlodipine 5 mg, prednisolone 7.5 mg, omeprazole 20 mg, simvastatin 10 mg, amitriptyline 25 mg, pregabalin 100 mg, losartan 50 mg and etanercept 50 mg every other week.

In January 2015, the patient was admitted in the Rheumatology Department for marked asthenia and persistent changes in liver tests lasting for two months (AST 251 U/L; ALT 650 U/L ; GGT 552 U/L ; AP 132 U/L ; bilirubin and albumin levels and coagulation test were normal). He had no other symptomatology and no relevant findings in the physical examination. No significant improvement in liver tests was observed after suspension of simvastatin one month before.

The patient denied intake of new drugs or dietary supplements, as well as herbal products. He usually lived in the rural environment, with daily contact with animals, including pigeons, cats, dogs and chickens. He referred consumption of drinking water and pasteurized dairy products. Regarding other investigation procedures, the imaging studies, including ultrasound and computed tomography (CT) showed a liver of normal size and morphology, with probable hepatic steatosis. Additional study of chronic liver diseases revealed negative serologies for hepatitis A, hepatitis B, hepatitis C, human

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immunodeficiency virus, and epstein-barr virus, with IgG positivity and IgM negativity for cytomegalovirus. Immunological study revealed positivity for anti-nuclear antibodies (title 1/320, nuclear pattern), which were already positive in several previous measurements,and negative results for anti-native double strand DNA, anti-phospholipids, anti-histone, anti-mitochondrial, anti-smooth muscle, anti-extractable nuclear antigens, anti-liver kidney microsomal, anti-liver cytosol 1 and anti-soluble liver antigen. Additionaly, transferrin saturation and serum levels of ferritin, alpha-1 antitrypsin and ceruloplasmin levels were normal.

Percutaneous liver biopsy was performed due to the absence of an evident cause for the changes in liver tests. Histopathological evaluation revealed moderate portal fibrosis without fibrous septation, with the presence of focal macrovesicular steatosis, inflammatory linfoplasmocitic infiltrate of moderate density with interface activity of variable intensity, and absence of cholestasis or hepatocellular siderosis (Figure 1). Granulomas centered by hyaline material in portal spaces were remarkable (Figure 2). Search for amyloid protein (Congo's red) and acid-fast bacilli (Ziehl-Neelsen) was negative.

Consequently, we performed an etiologic study for granulomatous diseases, including: chest CT scan, with no relevant findings; screening for *Mycobacterium tuberculosis* latent infection, which revealed negative tuberculin skin test and positive interferon gamma release assay; serum levels of angiotensin-converting enzyme, wright's reaction, search for serum cryptococcal antigen and serologies for *Coxiella burnetii* and toxoplasmosis, which were all normal or negative. Finally, the search for *Mycobacterium tuberculosis*, *Bartonella* and *Coxiella Burnetii* by molecular analysis in the liver tissue was negative.

Due to the persistence of liver tests abnormalities, it was decided by a multidisciplinary team to suspend etanercept, with a subsequent gradual improvement of analytical parameters and finally normalization three months later (Figure 3). The temporal relationship between the discontinuation of the drug and normalization of the liver tests is a possibility of a cause-effect relationship that could not be explained by another reason.

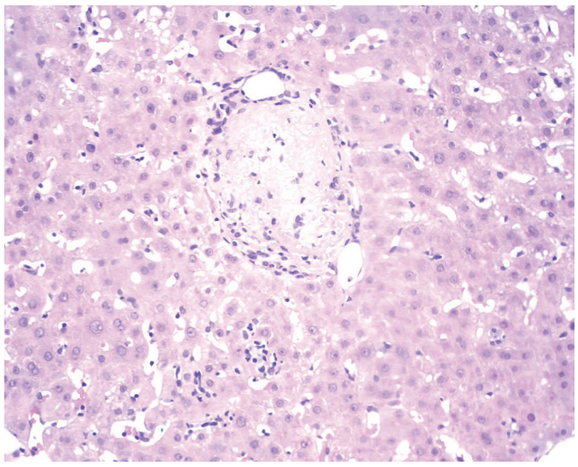

Fig. 1. — Lymphocytic inflammatory infiltrate of moderate density within portal spaces, with interface activity of variable intensity. HE x 200.

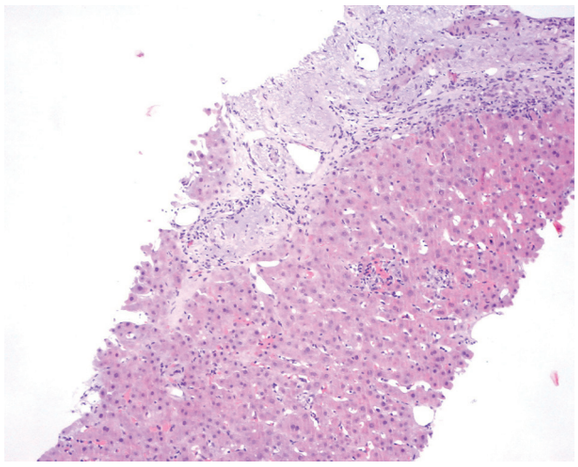

Fig. 2. — Hepatic granulomas centered by hyaline material were distributed randomly within the portal tract and lobules. HE x 200.

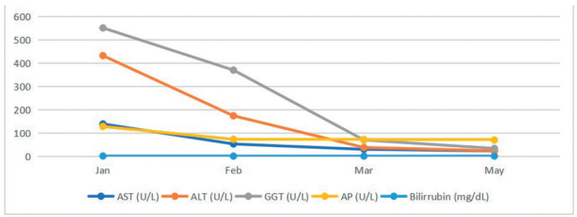

Fig. 3. — Evolution of liver tests after discontinuation of Etanercept.

Discussion

We report the development of granulomatous hepatitis in a patient during etanercept therapy for RA. Granulomas can be present in the liver in a variety of conditions, and although granulomas rarely cause structural liver damage, it is important to identify underlying systemic diseases, since it may have prognostic and therapeutic implications. Drug-induced granulomatous hepatitis usually presents with noncaseating epithelioid granulomas located in periportal or portal areas, and its diagnosis is challenging (9). This injury is usually transient and causes no sequelae. The drugs more frequently implicated include sulfonamide, sulfonylurea, phenytoin, quinidine, hydralazine, allopurinol and carbamazepine (10).

TNF-alpha plays a critical role in many aspects of immune system development, immune response regulation, and T cell-mediated tissue injury. TNF-alpha has both proinflammatory and immunoregulatory properties: it is a critical growth factor for thymocytes and plays an important role in the peripheral immune system in antigen-presenting cell function and in regulating

Table 1. — **Characteristics of the patients comparing the case reported with that previously described in the literature**

Case	Age	Months of therapy	AST (U/L)	ALT (U/L)	GGT (U/L)	ALP (U/L)	Histology	Steroids	Time to recover (months)
Farah M, et al.[8]	28	17	72	162	302	267	Portal tracts expanded and showing an infiltrate of mixed chronic inflammatory cells and occasional bile ductular damage. Scattered noncaseating granulomata present in both portal tracts and hepatic parenchyma	Prednisone 3 mg	11
Our case	76	144	251	650	552	132	moderate portal fibrosis without fibrous septation, Focal macrovesicular steatosis, inflammatory linfoplasmocitic infiltrate of moderate density with interface activity of variable intensity, and absence of cholestasis or hepatocellular siderosis. Granulomas centered by hyaline material in portal spaces.	Prednisolone 7,5 mg	3

apoptosis of potentially autoreactive T cells (4). Potential mechanisms for autoimmune development in the context of TNF-alpha inhibition have been proposed. Granuloma formation occurs as a result of a Th1-type immune-response and is characterized by infiltrate of activated macrophages and $CD4^+$ T lymphocytes. Although a large variety of cytokines are produced under these conditions, TNF-alpha, as well as interferon-gamma, interleukins (IL)-12, and IL-18 play critical roles in driving the Th1 commitment in the course of the granulomatous process (10). Based on these physiological aspects, the anti-TNF-alpha therapy may be indicated in patients with refractory sarcoidosis (1,2). Paradoxically, a worsening or induction of sarcoidosis and other granulomatous reactions triggered by etanercept have been reported (3-7).

To date, only one case of granulomatous liver disease associated with an anti-TNF agent was described in the literature (8). It referred to a patient with rheumatoid arthritis who developed granulomatous hepatitis after taking etanercept with low dose steroids. Infectious and metabolic causes of liver disease were excluded and the liver biopsy was not typical of sarcoidosis. Liver enzyme abnormalities improved after etanercept discontinuation.

Comparing that case to ours, we found many similarities (Table 1). Since the granulomatous disease is a reaction mediated by the adaptive immune system, the time elapsed between the introduction of the anti-TNF agent and the alteration of the liver tests can be very variable, which may justify the difference in the two cases described. In the case initially reported, the normalization of the analytical alterations was longer, which can be explained by the lower dose of steroids to which it was submitted in comparison with our patient, being the steroids effective in the resolution of granulomatous hepatitis for other causes. There are also similarities between other previous cases with granulomatous diseases associated with etanercept treatment (3).

After the exclusion of the main causes of chronic hepatitis and simvastatin withdrawal, we decided to perform a liver biopsy and it was the presence of non-caseating granulomas in portal spaces that warranted further etiologic study, that was normal. Therefore, it was decided to suspend etanercept therapy, with consequent normalization of liver tests. In previous reports, steroids have been added to the anti-TNF agent withdrawal (3), but our patient was already under chronic therapy with low dose prednisolone. This case also raises the question whether the development of granulomatous processes associated with anti-TNF agents, including etanercept, can be underdiagnosed due to the concomitant prescription of other immunosuppressant therapies, namely steroids.

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